GATTEX® (TEDUGLUTIDE [rDNA ORIGIN]) FOR THE TREATMENT OF ADULT PATIENTS WITH SHORT BOWEL SYNDROME (SBS) TO IMPROVE INTESTINAL ABSORPTION OF FLUID AND NUTRIENTS

BRIEFING DOCUMENT FOR THE GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEETING

MEETING DATE 16 October 2012

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table of Contents

List of Tables

List of Figures

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase, equivalent to SGPT
ALX-0600	Teduglutide
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase, equivalent to SGOT
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve from time zero to infinity
BMI	Body mass index
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
CI	Confidence interval
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450
CTD	Common Technical Document
DPP-IV	Dipeptidyl peptidase IV
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FCE	Fluid Composite Score
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GLP-2	Glucagon-like peptide-2
GLP-2R	Glucagon-like peptide-2 receptor
GH	Growth hormone
HLGT	High-level group term
HLT	High-level term
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed consent form
ICH	International Conference on Harmonisation
IGF	Insulin-like growth factor
IND	Investigational New Drug
I/O	Intake and output

IPN	Intravenous parenteral nutrition
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
KGF	Keratinocyte growth factor
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NOEL	No Observable Effect Level
NPS	NPS Pharmaceuticals, Inc.
NT,PBO/TED	Not treated, placebo/teduglutide group (Study 021)
PK	Pharmacokinetics
PN	Parenteral nutrition: includes fluids and electrolytes, and may include energy and micronutrients
PNALD	Parenteral nutrition-associated liver disease
PN/IV	Parenteral nutrition/intravenous fluid
PT	Preferred term
QOL	Quality of life
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
rDNA	Recombinant deoxyribonucleic acid
RBC	Red blood cells
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SAP	Statistical analysis plan
SBS	Short bowel syndrome
SC	Subcutaneous
SCS	Summary of Clinical Safety
SD	Standard deviation
SEM	Standard error of the mean
SF-36	36-item Medical Outcome Survey
SOC	System Organ Class
$t_{1/2}$	Elimination half-life
TED/TED	Teduglutide treated group (Study 021)
TPN	Total Parenteral Nutrition
US	United States
ULN	Upper limit of normal
WBC	White blood cells

EXECUTIVE SUMMARY

GATTEX® (teduglutide [rDNA] powder for subcutaneous injection) is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2) that increases intestinal absorptive capacity, resulting in increased fluid and nutrient absorption. NPS Pharmaceuticals (hereafter NPS) received Orphan Drug designation for teduglutide on June 29, 2000 and subsequently submitted a new drug application (NDA) to the Food and Drug Administration (FDA) on 30 November 2011, seeking approval of GATTEX for the treatment of adult patients with Short Bowel Syndrome (SBS) to improve intestinal absorption of fluid and nutrients. The recommended dose of GATTEX is 0.05 mg/kg administered once daily by subcutaneous injection. As part of the overall risk management plan (RMP) strategy, NPS will utilize the full prescribing label (Contraindications, Warnings & Precautions and language describing screening/and follow up testing) along with an SBS registry and a GATTEX Risk Evaluation and Mitigation Strategy (REMS) program, which will focus on communicating the product's potential risks to prescribers.

Unmet Medical Need in SBS

SBS is caused by a reduction in intestinal surface area, leading to inadequate absorptive capacity. SBS typically follows major surgical resection of the small intestine sometimes including parts or the entire colon. Rarely, SBS also occurs secondary to congenital intestinal abnormality or underlying intestinal disease. Because of the reduction in surface area, sub-optimized GI function occurs directly leading to reduced absorption of macronutrients, water, and electrolytes, leaving many at risk for malnutrition, diarrhea, dehydration, and weight loss. The extent of nutrition and fluid needs in SBS patients is dependent upon multiple factors including the amount of residual intestine and colon, presence of an ileal segment, and degree of spontaneous intestinal adaptation following resection (Dudrick et al, 1991; O'Keefe et al, 2006; Nightingale, 1999; Rombeau and Rolandelli, 1987; Scolapio et al, 1999; Shanbhogue and Molenaar, 1994; Vanderhoof and Langnas, 1997; Wilmore et al, 1997).

Following surgery, some degree of intestinal adaptation is expected in most patients. However, most patients require initial PN/IV support and many patients still require permanent PN/IV therapy. In SBS patients most intestinal adaptation (increase in absorption and decrease in GI fluid loss) occurring in the remnant intestine occurs within the first 6 months after surgery. However, a gradual adaptation may occur during and up to an additional 18 months. Consequently, spontaneous complete weaning of PN/IV is rare after six months and is unlikely to happen beyond 2 years.

Thus, SBS patients who continue to require PN/IV therapy beyond 2 years after the surgery causing SBS are unlikely to experience complete independence of parenteral nutrition and fluid support (Buchman, 1997). In a follow up study of SBS patients treated at a United Kingdom referral center, no patients were weaned from PN/IV therapy more than 5 years after the surgery that caused SBS (Lloyd et al, 2006).

For many patients then, SBS is a lifelong disease that is associated with significant increases in morbidity and mortality, particularly in patients requiring chronic PN/IV therapy. In the United States (US), there are about 10,000 to 15,000 adult SBS patients requiring chronic parenteral nutrition/intravenous fluids and electrolytes [PN/IV] support (Oley Foundation for Home Parenteral and Enteral Nutrition Registry, 1992 and the American Society for Parenteral and Enteral Nutrition). Chronic PN/IV therapy is typically given 5-7 days a week for about 10 or more hours per day.

While lifesaving in many SBS patients with intestinal failure, chronic PN/IV treatment is associated with increased morbidity and mortality (Messing et al, 1999; Scolapio et al, 1999). Catheter-related infections at the insertion site or tunnel can lead to bacteremia and septicemia. Central venous thrombosis and/or thromboembolism are also significant risks associated with chronic PN/IV therapy (Buchman et al, 2003; DeLegge et al, 2007; Jackson and Buchman, 2005; Jeppesen, 2006). Liver disease (and eventual liver failure) is common among SBS patients being treated with PN/IV, more so than in many other patient types on parenteral nutrition (Cavicchi et al, 2000). Liver disease is one of the main causes of death in patients with permanent intestinal failure. In a prospective cohort

study, the prevalence of complicated liver disease among patients receiving home parenteral nutrition for permanent intestinal failure was 26% at 2 years, 39% at 4 years, 50% at 6 years, and 53% at 8 years.

Psychosocial co-morbidities are highly prevalent in patients with SBS intestinal failure. Rates of anxiety and depression are much higher than in the general population, especially in those with increased GI fluid losses and chronic diarrhea. Anxiety, depression, and the other associated morbidities limit these patients' ability to live normal lives. Most SBS patients who require chronic PN/IV therapy are unable to sustain employment (Baxter et.al, 2006; Winkler et al, 2010; Nørholk 2012).

The current management strategy in SBS is a combination of specialized diets, anti-diarrheal, anti-secretory agents, and parenteral nutrition/IV fluids to meet the needs of SBS patients and calls upon the support of a team of healthcare professions including not only the physician, but the pharmacist, dietician and home care nurses. To date, there is no targeted long-term treatment aimed at optimizing intestinal absorption of fluids and nutrients and decrease intestinal fluid and nutrient loss. For SBS patients on chronic PN/IV the goals of intestinal rehabilitation include decreasing the need for PN/IV and, ideally, weaning patients completely off PN/IV therapy while promoting enteral feeds and maintaining clinical status. Increasing the time off from PN/IV therapy may also decrease the burden of illness suffered by SBS patients.

Intestinal transplantation is currently the only therapeutic option to restore lost absorptive capacity, but it is associated with high morbidity and mortality. Patients considered potential candidates for intestinal transplant include those with recurrent central line infections, loss of vascular access, or complications of longstanding PN/IV support, such as progressive liver disease.

No current long-term medical treatment optimizes intestinal absorption. The ideal goal of intestinal rehabilitation is to increase intestinal absorption of orally ingested fluids and nutrients, allowing an opportunity for SBS patients to be completely weaned from long-term PN/IV therapy. A reduction in the volume of PN/IV and number of hours per

day or days per week necessary for chronic PN/IV therapy can lead to significant benefits in SBS patients even if complete weaning is not possible.

NPS developed GATTEX to fulfill the unmet need for a long-term treatment that could optimize remnant intestinal function in SBS patients. GATTEX treatment provides increased absorption of fluids and nutrients; allows for patients to gain additional days off PN/IV therapy; and increases the likelihood of complete weaning patients from chronic PN/IV therapy.

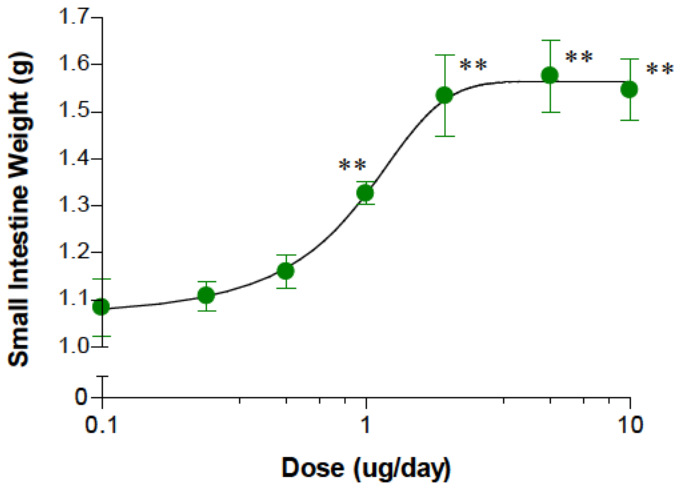
Overview of GATTEX

GATTEX is an analog of naturally occurring human GLP-2 that increases intestinal absorptive capacity, resulting in increased fluid and nutrient absorption. GATTEX differs from GLP-2 in the substitution of glycine for alanine at the second position of the N-terminus. The glycine substitution results in resistance to degradation by dipeptidyl peptidase-IV (DPP-IV) (Tavares et al, 2000), extending the pharmacodynamic activity of GATTEX. GATTEX binds to the GLP-2 receptors (GLP-2R), located in subpopulations of enteroendocrine cells, subepithelial myofibroblasts, and enteric neurons of the submucosal and myenteric plexus with receptor activation releasing intermediary growth factors locally, which act on epithelial cells.

Nonclinical Pharmacodynamics

Following once daily dosing, teduglutide increased small intestinal weight in mice in a dose-dependent manner, beginning 4 days after initiation of treatment and reaching a plateau between days 7 and 14 of treatment (Figure 1). In animal models of short bowel resection, teduglutide increases nutrient absorption and expands mucosal surface area (Scott et al, 1998; Sigalet and Martin 2000). Similar to GLP-2, teduglutide promotes growth and repair of gastrointestinal (GI) epithelium in animal models of TPN-induced intestinal hypoplasia, short bowel resection, and in models of induced and spontaneous GI damage and dysfunction.

Figure 1. Increase in Small Intestinal Weight with Teduglutide



** p < 0.01 compared to the vehicle control group

Clinical Pharmacokinetics and Pharmacodynamics

In humans, GATTEX is rapidly absorbed from subcutaneous (SC) injection sites; with maximum plasma levels occurring approximately 3-5 hours after dose administration at all dose levels. The absorption of GATTEX is dose proportional at single and repeated SC doses up to 50 mg (Study CL0600-022). The absolute bioavailability of SC GATTEX is high (88%). GATTEX is most likely metabolized by hydrolytic degradation, resulting in smaller peptide fragments and amino acids. GATTEX has an elimination half-life of approximately 2 hours. In subjects with moderate or severe renal impairment or end-stage renal disease, systemic exposure to GATTEX increases with increasing levels of renal impairment, therefore, the proposed label suggests dose adjustment in these patients.

Increased capacity to absorb fluids and nutrients with GATTEX, as observed in nonclinical studies, is consistent with the goals of intestinal rehabilitation for SBS

patients. Rehabilitation includes optimizing remnant GI function as well as decreasing GI fluid losses and, when possible, minimizing exposure to PN/IV constituents.

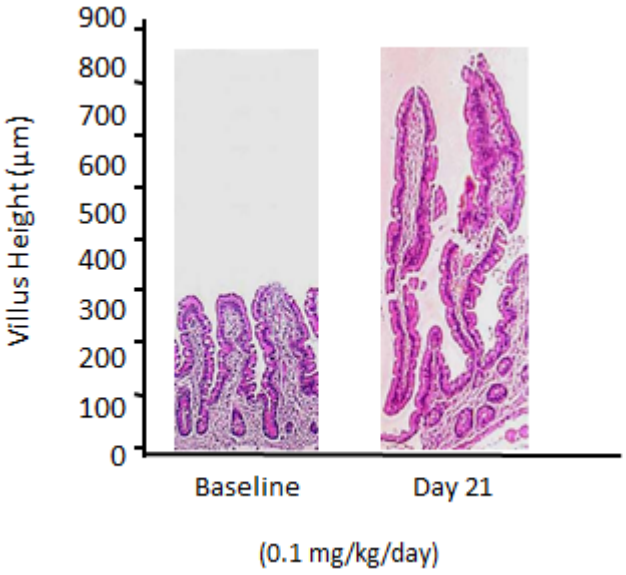
NPS designed the GATTEX development program to affirm clinically significant increases in intestinal function. One challenging aspect in studying changes in intestinal function and absorptive capacity in SBS patients is how to measure clinical improvement. Physiologically, intestinal absorption directly correlates to the difference between fluid intake (oral + PN/IV) and output (urinary and fecal/stomal). The GATTEX clinical development program used this relationship to define changes in intestinal absorptive capacity, specifically by tracking oral and PN/IV volume versus urinary and, in one study, fecal/stomal output in study subjects.

The intestinal absorptive effects of GATTEX were first evaluated in the clinical pharmacology Study ALX-0600-92001 (hereafter referred to as Study 92001) that collected detailed information on intestinal absorption and intestinal surface area. The study specifically examined changes in urinary output and fecal/stomal output as measures of absorption while keeping intake stable (oral + PN volumes) during each of 3 controlled inpatient visits.

Study 92001 enrolled 17 adult subjects with stable SBS due to various underlying etiologies and with diverse intestinal remnant anatomies. The subjects were treated with GATTEX at doses of 0.03, 0.1, and 0.15 mg/kg/day for 21 days and were then followed for 21 days off treatment. During 3 admissions to a metabolic research unit (at baseline, end-of-treatment, and end of follow-up), 72-hour nutrient absorption testing was performed to evaluate effects of GATTEX administration on absolute and relative absorption as well as stomal or fecal output of fat, nitrogen, sodium, potassium, calories, and GI fluid. Endoscopies were also performed to obtain intestinal biopsy samples for histopathological examination. The protocol mandated that subjects have no change in their PN/IV volume requirements and have individualized diets to maintain constant caloric intake during these 72-hour admissions so that changes in fecal wet weight and composition and urinary output would be reflective of changes in absorption.

GATTEX increased villus height and crypt depth in the intestinal mucosa (illustrative results for 1 subject shown in Figure 2). In addition, GATTEX increased absorption of important nutritional parameters (fat, nitrogen, sodium, potassium, calories, GI fluids), as measured by fecal wet weight obtained through stool balance studies, with corresponding decreases in fecal and stomal loss of these key nutrients and calories. GATTEX increased absolute GI fluid absorption by almost 900 mL per day and decreased GI fluid losses (fecal or ostomy output) by approximately the same amount (-887 mL/24 hours) (each $p<0.001$ vs. baseline), representing approximately a 30% reduction in fecal losses from baseline in these SBS subjects and correlating with an increase in urine output of 508 mL/day ($p<0.001$ vs. baseline). Since intake was kept stable (no change in PN/IV volume and standardized diets), increased intestinal fluid absorption was reflected in both decreased GI fluid losses and increased urine output.

Figure 2. Increased Intestinal Villus Height and Crypt Depth in an SBS Subject Treated with GATTEX

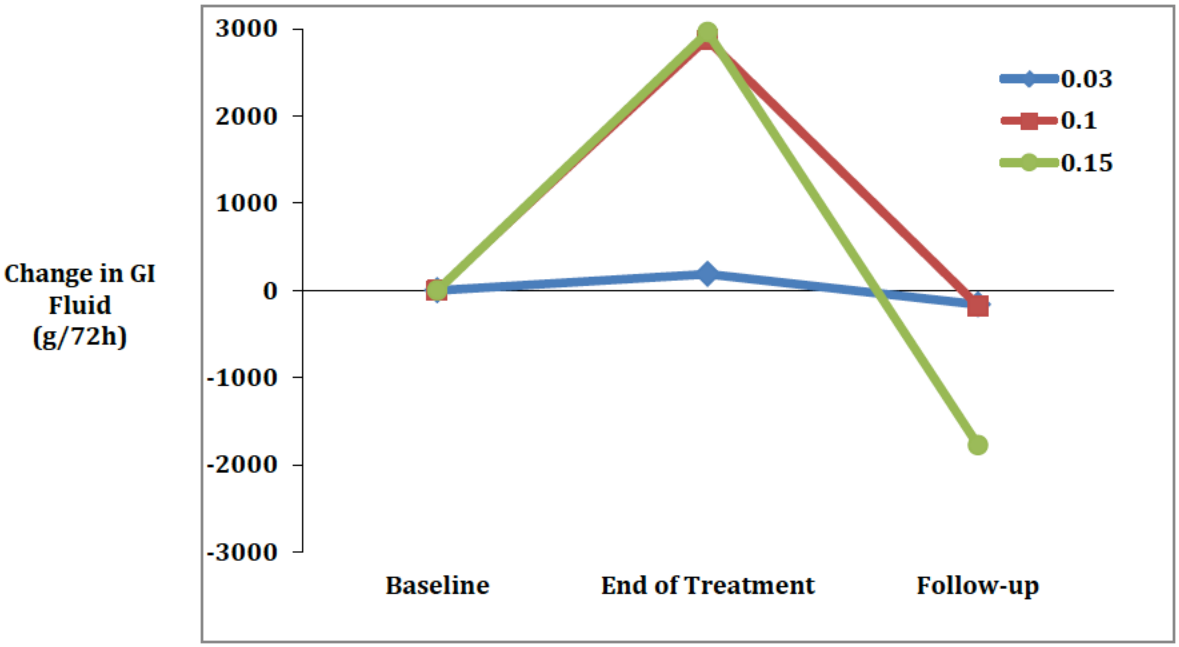


Both the 0.10 and 0.15 mg/kg/day dose groups produced significant increases in fluid and nutrient absorption, but there was no difference between the 0.15 mg/kg/day dose and the

0.10 mg/kg/day dose. There was less evidence to determine an effect from the 0.03 mg/kg/day dose.

Finally, as shown in Figure 3, the gains in absorption during treatment with GATTEX were reversed after GATTEX discontinuation, underscoring the observed effects were GATTEX dependent.

Figure 3. Changes in GI Fluid Absorption During and After Withdrawal of GATTEX Treatment (Study 92001)



In summary, Study 92001 demonstrated a beneficial effect of GATTEX on intestinal function, with data supporting potential clinical benefit and use of the 0.10 mg/kg/day dose for evaluation in phase 3.

Design of Phase 3

NPS evaluated the pharmacodynamic effect of GATTEX in Study 92001 by specifically measuring increased intestinal absorption of fluids and nutrition, increases in surface area, and decreases in fecal fluid loss and increased urine output. The reproducibility of

these complex evaluations, which were conducted during admissions to a metabolic research unit, in a multinational setting presents unique challenges, especially so in the study of orphan populations. Therefore, NPS sought to design its phase 3 studies using a more practical and clinically relevant outpatient design. Endpoint selection in this setting took into account assessments, which would be considered meaningful to SBS patients and clinicians. The endpoint selected was "at least a 20% reduction in PN/IV volume", which could represent a 1-day reduction per week in most patients. This endpoint was discussed with both the FDA and two SBS expert panels before inclusion in the design of phase 3 studies CL0600-004 (hereafter referred to as Study 004) and CL0600-020 (hereafter referred to as Study 020).

The primary endpoint in Study 004 was expanded to characterize more completely the reduction in PN/IV volume and included a description of both intensity and duration of response (graded categorical response), beginning as early as Week 16. A 20% or greater volume reduction responder definition was included as a key secondary endpoint. Following completion of Study 004, NPS met with the FDA in July 2008 to discuss the impact of the efficacy findings on further study development. In this discussion, FDA stated that a possible clinical effect for PN volume reduction from the 0.05 mg/kg/day dose was seen in Study 004 and accordingly one additional confirmatory study, not two, would be needed.

Following the FDA meeting, NPS designed Study 020 as a confirmatory trial of the 0.05 mg/kg/day dose. The primary endpoint was at least a 20% reduction in PN/IV volume achieved at both Weeks 20 and Weeks 24. The graded categorical response that was the primary endpoint in Study 004 was included as a secondary endpoint in the confirmatory Study 020. Additional secondary endpoints based upon PN/IV volume at Week 24 included: mean percent change from baseline, mean absolute change from baseline, duration of response, and the number of patients with at least a 1-day reduction.

Study 004 and Study 020 were similar in many design elements. Both were prospective, randomized, double-blind, placebo-controlled, parallel-group, multinational, and

multicenter studies. Both enrolled adults (≥ 18 years of age) with SBS secondary to intestinal surgery who were dependent on PN/IV support for at least 12 months and required PN/IV at least 3 times per week. Each was conducted in the US, Canada, and Europe and included a screening visit, optimization period, and stabilization period prior to randomization. Subjects who demonstrated PN/IV volume stability for at least 4 consecutive weeks were eligible for randomization. Study 004 included GATTEX doses of 0.10 mg/kg/day and 0.05 mg/kg/day while Study 020 included only 0.05 mg/kg/day.

In Study 004 and Study 020 subjects were asked to maintain stable oral intake so that increased intestinal fluid absorption would be reflected in increased urinary output. In the optimization and stabilization periods, baseline urine output was measured while subjects had consistent oral intake and stable PN/IV volume. Fecal output was not measured due to subject aversion. During the treatment period, subjects who had increased intestinal fluid absorption should have demonstrated increased urine output, allowing the investigator to reduce PN/IV volume in those who were deemed clinically stable. The protocol specified consistent oral intake so that reductions in PN/IV volume would reflect changes in fluid absorption.

In both studies, the investigators followed a weaning algorithm that was protocol defined and allowed PN/IV volume adjustments based on 48-hour urinary output and overall hydration and clinical status. However, there were significant differences in the algorithm used in each study. The Study 004 protocol limited the maximum amount by which PN/IV volume could be reduced to 10% beginning at Week 4 and then at monthly visits. This restriction was to ensure that subjects did not become dehydrated. Subsequently, in Study 020, PN/IV volume reductions could begin at Week 2, and be as high as 30% of the baseline level.

Efficacy Findings in Study 004

Both the 0.10 mg/kg/day and the 0.05 mg/kg/day doses of GATTEX had an effect in SBS patients leading to a 2.5 Liter reduction in PN/IV volume in both treatment groups compared to 0.9 Liter reduction in placebo-treated patients. However, because of a

higher baseline PN/IV volume the 0.10 mg/kg/day group failed to meet statistical significance for the primary endpoint (p=0.161), and because of the pre-specified hierarchical testing design, no further primary analysis was to be done on the 0.05 mg/kg/day dose.

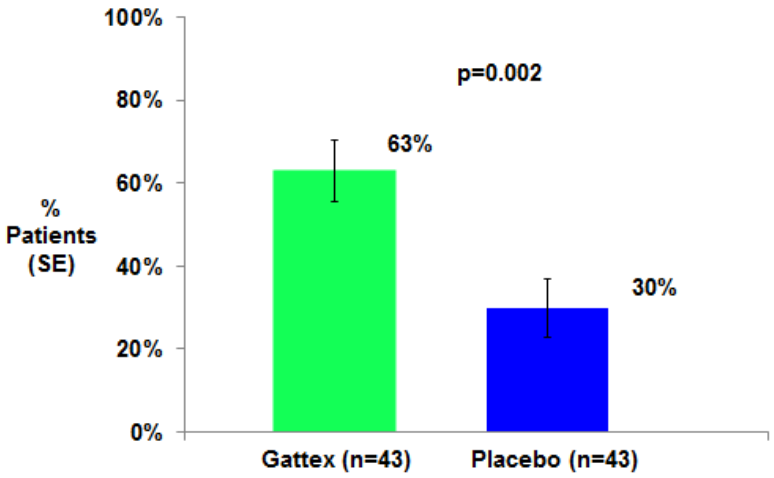
However, there was supportive evidence that the 0.05 mg/kg/day group had a clinically meaningful reduction in PN/IV therapy. The nominal p value compared to placebo in the 0.05 mg/kg/day group was 0.007 for the primary endpoint. For the responder analysis (at least 20% reduction at both Weeks 20 and 24, which is the primary endpoint in Study 020) in the 0.05 mg/kg/day group, the p value was 0.005. Two subjects weaned from PN/IV in the 0.05 mg/kg/d group versus none in placebo. At Week 24, a mean weekly PN/IV volume reduction of -2.5 L was observed in both active treatment groups compared to -0.9 L for placebo (p=0.08 for each comparison of active versus placebo).

In addition, findings from intestinal biopsies in Study 004 affirmed the pharmacodynamic effect of GATTEX, as both GATTEX doses induced expansion of the absorptive epithelium by increasing villus height in the small intestine (GATTEX 0.05 mg/kg/day [p=0.0065] and GATTEX 0.10 mg/kg/day [p=0.0024]). Thus, while the preplanned statistical testing failed on the first dose tested, there was significant secondary evidence that GATTEX produced a clinically meaningful effect in the 0.05 mg/kg dose group.

Efficacy Findings in Study 020

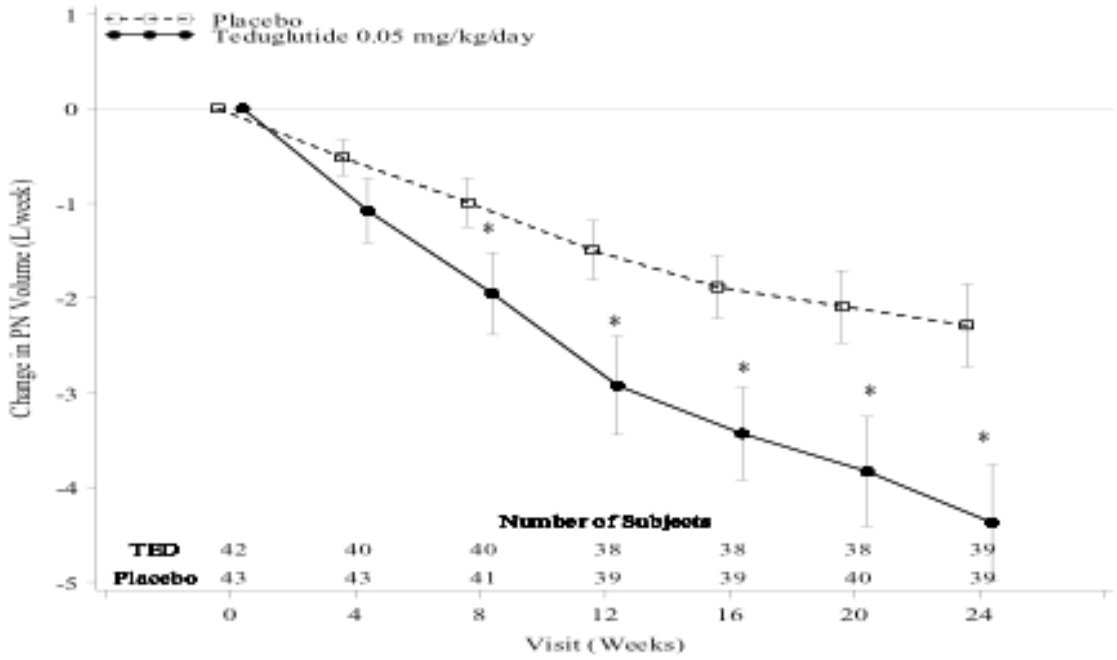
The primary endpoint in Study 020 was the 20% or greater responder analysis based upon Weeks 20 and Week 24. The responder rate in the 0.05 mg/kg/day treatment group (27/43 subjects, 62.8%) was more than 2-fold greater than that observed in the placebo group (13/43 subjects, 30.2%) (Figure 4). This difference was statistically significant (p=0.002).

Figure 4. Responder Rate – Study 020 (Intent-to-Treat Population)



The absolute change in fluid volume by week in Study 020 is shown in Figure 5. Robust differences from placebo emerged by Week 4 and persisted with longer duration of treatment. All secondary endpoints statistically favored GATTEX, including the ordered categorical response variable used as the primary endpoint in Study 004 (p=0.004).

Figure 5. Absolute Change in PN/IV Volume (L/week ± SE) – Study 020 (Intent-to-Treat Population)

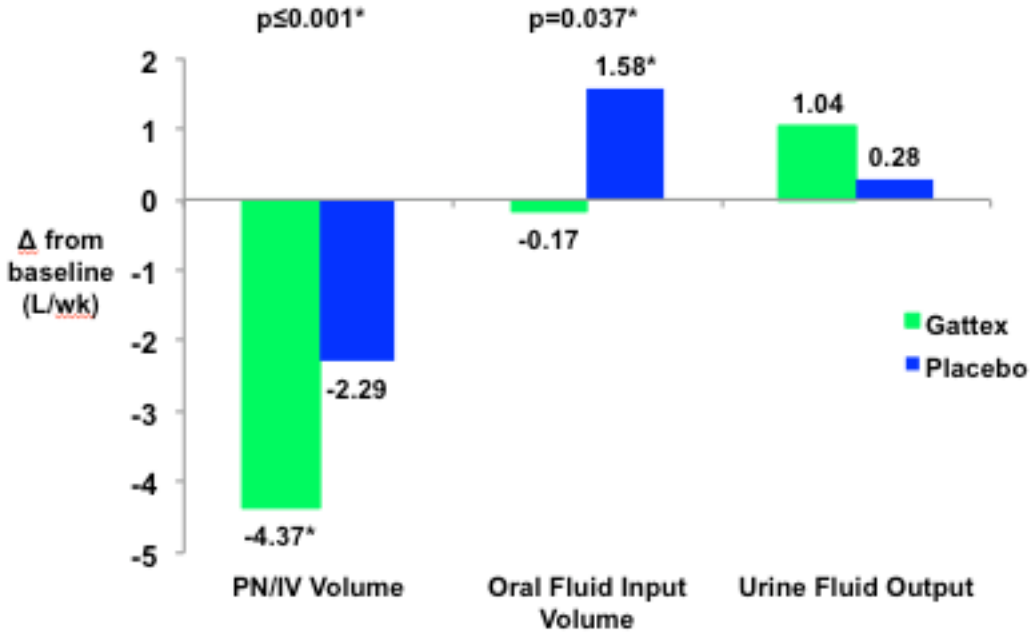


L=liter; PN=parenteral nutrition, SE=standard error, TED=teduglutide
* $p < 0.05$

Though the protocol specified that subjects should maintain a stable oral intake, placebo subjects increased their intake over the course of the study to compensate for their PN/IV volume reductions.

In contrast to the findings with placebo, GATTEX-treated subjects maintained stable oral intake over the 24-week study (results at Week 24 shown in Figure 6). In the setting of stable oral intake and PN/IV volume reduction with GATTEX, urine output continued to increase (results at Week 24 shown in Figure 6), indicating increased net fluid absorption. Even at the end of the trial, further weaning appeared possible in subjects treated with GATTEX (based on their increased urine output).

Figure 6. PN/IV Reductions With GATTEX vs. Placebo at Week 24 – Study 020



The significant PN/IV volume reduction translated into additional clinical benefit. Weekly PN/IV support at Week 24 was reduced by 1 or more days in over half of the subjects who completed this trial in the GATTEX group (53.8% [21/39 subjects]) vs. 23.1% (9/39) of placebo subjects (p=0.005). Post hoc analyses were conducted at Week 52 looking at ≥2 and ≥3 additional days off per week: 8 (of 39, 21%) GATTEX-treated subjects required ≥2 fewer days per week of PN/IV support, compared to 3 (of 39, 8%) placebo subjects. An additional 4 (of 39, 10%) GATTEX-treated subjects required ≥3 fewer days per week of PN/IV support, compared to 2 (of 39, 5%) placebo subjects.

Efficacy Findings in Long-Term Extension Studies

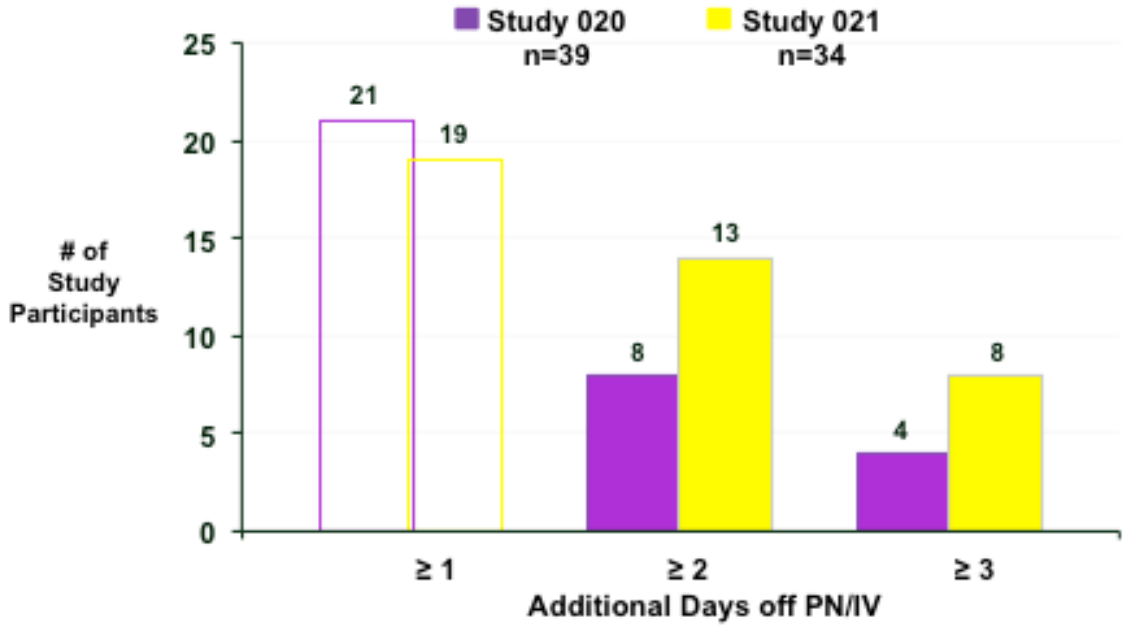
SBS subjects participating in the placebo-controlled trials of GATTEX were offered an opportunity to enroll into extension trials to further demonstrate sustained benefit associated with the long-term use of GATTEX. Study CL0600-005 (hereafter referred to

as Study 005) is a completed long-term extension study to Study 004 that enrolled subjects for an additional 28 weeks. Study CL0600-021 (hereafter referred to as Study 021) is an ongoing extension study of Study 020 in which GATTEX 0.05 mg/kg/day is being evaluated for up to 2 years. Of note, more than 90% of SBS subjects who completed their participation in a placebo-controlled trial of GATTEX elected to continue treatment in a long-term extension study.

Of 34 subjects in Study 021 who have been treated with GATTEX for at least 1 year (6 months in Study 020 and 6 months in Study 021), 31 (72% of the original 43 subjects treated in Study 020) were determined to have a clinical response at 1 year (i.e., ≥20% reduction from baseline), including all 25 GATTEX responders in Study 020 and 6 of 9 subjects who did not meet responder status at month 6 in Study 020.

Long-term treatment with GATTEX resulted in an additional reduction in the number of days (defined as a 24 hour calendar day) per week that PN/IV was required. Most SBS PN/IV-dependent patients require on average 5 to 6 days of PN/IV per week; one additional day off represents approximately a 20% reduction in PN/IV volume. A reduction in PN/IV support of at least 2 days per week was achieved in 13 (of 34, 38%) subjects after treatment with GATTEX for 1 year (vs. 8 of 39 subjects, 21% after 6 months in Study 020) (Figure 7). A reduction in PN/IV support of at least 3 days was achieved in 8 (of 34, 24%) subjects after treatment with GATTEX for 1 year (vs. 4 of 39 subjects, 10%, after 6 months in Study 020).

Figure 7. Additional Days Off PN/IV with 6 Months Additional Exposure to GATTEX in Long-term Extension Study 021



GATTEX Patients Who Are Completely Weaned from PN/IV Therapy

Across the phase 3 studies, as of the April 11, 2012 amendment to the NDA, 10 of 134 subjects treated with GATTEX 0.05 mg/kg/day were weaned completely from PN/IV therapy. Subjects were weaned from PN/IV as early as 3 months and as late as 27 months after initiation of GATTEX, suggesting that long-term use is associated with continued improvement. Specific information on subjects who have completely weaned is presented in Table 1.

Table 1. Summary of SBS Subjects Who Permanently Discontinued PN/IV Treatment

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6[a]	Subject 7	Subject 8	Subject 9	Subject 10
Original Study	004	004	004	020	020	020	020	020	020	020
GATTEX dose (mg/kg/day)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Age (years), gender	61, M	54, M	66, M	50, M	46, F	41, F	55, F	66, F	39, M	69, F
Reason for resection	Mesenteric infarction	Mesenteric venous infarction	Ischemic bowel	Ulcerative colitis	Crohn's disease	Injury	Micro-vascular, unknown process	Enteritis radio-therapy	Injury	Mesenteric arterial infarction
Colon in continuity	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Remaining small intestine (cm)	80	28	48	250	250	55	46	80	50	120
Duration of PN/IV dependency (years) at time of discontinuation	6.5	25	2	1.5	1.5	2	10	7	13	5.25
PN/IV requirement at baseline (L/week)	3.5	5.4	12	13	3.5	5.6	4.95	4.35	6.75	3.5
PN/IV requirement at baseline (days/week)	4	3	6	6	3	6	3	3	3	3
Duration of GATTEX treatment at the time of PN/IV wean-off (weeks)	12	16	52	32	28	78	87	89	75	101
Duration of independence from PN/IV at the time of data cut-off (weeks)	48[b]	41[b]	3[b]	84[b]	88[b]	12[b]	0[c]	14[c]	13[c]	0[c]

L=liters; PN/IV=parenteral nutrition/intravenous hydration

[a] Subject 6 initially on placebo in 020; [b] Completed study; [c] Data cutoff = 31 May 2012

In the phase 3 studies with GATTEX, subjects had an average of 6 years from their putative surgery leading to SBS and were therefore considered to have permanent dependence on PN/IV support. Spontaneous weaning in this population is a highly unlikely; therefore, 10 subjects treated with 0.05 mg/kg/day who were weaned from PN/IV therapy is strongly supportive of GATTEX efficacy as well as consistent with long-term improvement in intestinal function caused by GATTEX.

Summary of GATTEX Efficacy

In summary, GATTEX significantly increases intestinal function with resulting increased absorption of fluids and nutrients. The effect is clinically beneficial to adult SBS patients. Specifically, GATTEX:

- increases intestinal surface area, as demonstrated by direct biopsy data
- increases nutrient absorption, as demonstrated in stool balance studies
- decreases GI fluid losses, as measured in strict controlled inpatient evaluations, and
- increases in intestinal fluid absorption, as measured by changes in intake and output while on a standardized diet

These targeted effects in the intestine translate into clinical benefit as follows:

- GATTEX-treated subjects experienced, on average, a 40% reduction in PN/IV volume from baseline at 6 months
- 54% of GATTEX-treated subjects experienced additional days off PN/IV support at 6 months
- PN/IV volume reductions and additional days off are sustained over time with GATTEX, with almost 25% of subjects now experiencing at least 3 additional days off/week of PN/IV at 1 year

- Ten GATTEX-treated subjects receiving 0.05 mg/kg/day were completely weaned off their PN/IV after 3 to 27 months.
- For GATTEX patients who are now independent of PN/IV, this allows for the removal of the central line and elimination of the risks associated with central lines and parenteral nutrition including sepsis, liver disease, and thrombosis.

Safety Findings Across Development

Nonclinical

The nonclinical safety evaluation package (acute, repeated dose, cardiovascular, reproductive toxicology, juvenile animal, carcinogenicity, genotoxicity, and additional support studies) was performed to provide a comprehensive safety evaluation of teduglutide at the proposed doses used in the clinical studies.

Nonclinical studies have shown that teduglutide pharmacologic effects are localized to the digestive tract. The pattern of toxicity has been extremely consistent amongst the various species studied, with the majority of the findings being associated with the pharmacological activity of teduglutide or with an exaggerated / extended pharmacology. In all species, pharmacological effects were noted at all dose levels and consisted of increased weight and length of the small and/or large intestine, which correlated microscopically with mucosal hyperplasia and/or hypertrophy in these organs. These findings are considered to represent an extension or exaggeration of the pharmacology of the drug. They were not associated with any relevant changes in clinical chemistry parameters indicative of any dysfunction. At the injection site, inflammation was a common finding.

In a nonclinical rat carcinogenicity study, no treatment-related malignant tumors were observed, but there were statistically significant increases in benign tumors of the bile duct epithelium and adenomas of the jejunal mucosa in male rats. The NOEL for the benign neoplasms was 9.8 times the human exposure at 0.05 mg/kg/day.

Preliminary results in a mouse carcinogenicity study showed the presence of jejunal adenocarcinoma with minimal epithelial hyperplasia without adenoma. Jejunal adenocarcinoma is a rare tumor in Crl:CD1 (ICR) mice and therefore the occurrence in high-dose males (at 12.5 mg/kg/day) may be test article related. This dose represents an exposure level 150 (AUC) and 480 (C_{max}) times the recommended human dose of 0.05 mg/kg/day.

In the literature, synthetic Gly-GLP-2 (with same amino acid sequence as GATTEX but different manufacturing process) promoted growth of existing cancer in tissue that was exposed to known carcinogens in the mouse rodent intestine. However, this finding was inconsistent with findings in a xenographic mouse model of colon cancer, and other models where GLP-2 failed to stimulate growth of cancer cells (Thulesen et al, 2004; Iakoubov et al, 2009; Koehler et al, 2008).

The nonclinical findings will be addressed through the proposed label, an SBS registry, and the Risk Management Plan which includes a REMS. The nonclinical program demonstrates an acceptable toxicological profile for teduglutide and supports the currently planned clinical dose of 0.05 mg/kg/d for adults with PN-dependent SBS.

Clinical

The clinical safety database for the GATTEX Development Program includes data from 15 studies: 9 clinical pharmacology studies; 4 phase 3 studies in adult subjects with SBS; and 2 exploratory studies in subjects with active Crohn's disease. As of 30 June 2011, all studies were complete with the exception of Study 021, a phase 3 two-year extension study in adult subjects with PN-dependent SBS.

A total of 566 subjects were treated with GATTEX and 198 subjects were treated with placebo. Of the 566 subjects treated with GATTEX, 299 subjects were treated in the Clinical Pharmacology Studies, 173 subjects were treated in SBS phase 3 studies, and 94 subjects were treated in Other Studies (active Crohn’s disease). The 2 SBS double-blind,

placebo-controlled studies are the largest controlled studies ever conducted in subjects with SBS.

Across development, GATTEX has been well tolerated with low discontinuation rates (17% in the phase 3 SBS studies). The adverse event (AE) profile is generally consistent with the expected GI pharmacodynamic effects, with GI AEs the most likely events. The most common treatment-emergent AEs with GATTEX (>15%) in the placebo-controlled SBS studies (and occurring at a frequency higher with GATTEX vs. placebo) were abdominal pain, upper respiratory tract infections, nausea, injection site reactions, abdominal distension, headaches, and gastrointestinal stoma complication. Of note, diarrhea, which is a main complaint of SBS patients, was more commonly reported in placebo subjects (11.9% vs. 6.4% with GATTEX). Mean (SD) weight gain from baseline of 1.06 (2.99) kg was measured at endpoint among GATTEX-treated subjects, as compared to mean weight loss of -0.26 (2.81) kg with placebo. Injection site reactions occurred in 11.7% (9/77) of subjects with 0.05 mg/kg/day vs. 11.9% (7/59) of placebo subjects.

NPS nonclinical studies have shown that teduglutide pharmacologic effects are localized to the digestive tract. Accordingly, the intestine, the biliary tract and pancreas are areas of special interest.

Given the intestinotrophic effects of GATTEX, intestinal biopsy specimens were collected at baseline and at Week 24 in Study 004 to determine morphometric features of the mucosal architecture. No histological evidence of dysplasia or malignancy was observed in any of the 227 intestinal specimens (from 77 subjects: 15 placebo, 32 GATTEX 0.05 mg/kg/day, 30 GATTEX 0.10 mg/kg/day). In addition, the protocol demanded colonoscopies in patients that terminated the clinical SBS studies revealed GI polyps in 5 subjects, three who had adenomatous polyps and two who had hyperplastic polyps.

Across development 3 cases of cancer have been reported, 2 of which resulted in death. A 47-year-old man died of metastatic adenocarcinoma of unknown GI origin 11 months

after the start of GATTEX. The subject had a history of Hodgkin's disease diagnosed more than 20 years earlier that was treated with chemotherapy and radiotherapy to his abdomen, which are known to predispose to development of secondary malignancy. Radiation enteritis led to intestinal resection and SBS. While the investigator considered the cancer related to GATTEX, there was a focal lesion of unclear origin in an enlarged liver on CT prior to initiation of GATTEX treatment.

Two cases of lung cancer were reported in subjects with a smoking history. In brief, a 64-year-old white male with a history of smoking (i.e., about 30 cigarettes/day for approximately 30 years) was diagnosed with non-small cell lung cancer after 87 days of GATTEX treatment. And, a 74-year-old male, with a history of smoking 10 cigarettes a day for about 5 years prior to stopping smoking approximately 25 years ago, was diagnosed with lung squamous cell carcinoma stage unspecified. The opinions of the investigators and oncology experts were that it was unlikely that GATTEX initiated these cancers.

Overview of Proposed Risk Management Program

NPS is committed to the safety of patients and believes that the appropriate use of GATTEX can be achieved through the proposed Risk Management Plan. As part of the overall risk management plan (RMP) strategy, NPS will provide an Education Program. NPS will utilize the full prescribing label (Contraindications, Warnings & Precautions and language describing screening/and follow up testing) along with an SBS registry and a GATTEX Risk Evaluation and Mitigation Strategy (REMS) program, which will focus on communicating the product's potential risks to prescribers, including risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and pancreatic and biliary disorders.

Proposed Labeling

Given the mechanism of action related to promotion of growth in GI tissue, published literature, and observations in the development, NPS cannot exclude the possibility that

GATTEX could accelerate the growth of existing intestinal neoplasms. For this reason, NPS will utilize its proposed label and REMS program communication plan to educate prescribers about the potential risks associated with GATTEX including GI polyps and malignancy. The proposed labeling includes the following contraindication.

> *GATTEX is contraindicated in patients with active malignancy and in patients with a history of malignancies within the last five years (excluding basal cell carcinoma).*

As per the proposed label, all patients treated with GATTEX with a colon (or remnant) must have full colonoscopy (or alternate imaging) and removal of polyps if found within the past 6 months. Complete colonoscopy (or alternate imaging) will be performed every 5 years or sooner depending on physician judgment and as recommended within current polyp follow-up guidelines. Because of possible risks for biliary or pancreatic duct obstructions, total, direct and indirect bilirubin, alkaline phosphatase, amylase, and lipase will be performed at baseline and then will be recommended every 6 months, with possible imaging if significant increases are seen.

SBS Registry

In addition, patients will be enrolled in an SBS registry, which will include data collection: baseline demographics, etiology, colonoscopy (or alternate imaging) and laboratory results; ongoing laboratory, colonoscopy and other imaging studies, as well as PN/IV requirement. Post discontinuation of GATTEX, patients will continue to be followed. The registry will be open to all SBS patients, but will focus on GATTEX- treated patients.

Education Program for Prescribers and Patients

NPS is proposing an education plan for prescribers and a medication guide to warn patients about the potential risks of using GATTEX. A Medication Guide will support this communication of risks and will be outside the REMS.

Proposed REMS

The proposed REMS is a plan that will support effective communication to prescribers about the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, GI obstruction and pancreatic and biliary adverse events. The communication plan will consist of a Dear Healthcare Provider Letter and a Dear Professional Society Letter.

Benefit-Risk Conclusion

As seen in Study 92001 GATTEX has substantial effect on GI absorption of fluids and nutrients, with a decrease in fluid loss (fecal/stomal output). This increase in absorption and decrease in loss translates into a significant reduction in the need for PN/IV therapy. In 2 phase 3, 24-week studies (004 and 020), a clinically significant reduction in the amount of PN/IV fluids was affirmed with a 0.05 mg/kg/day dose. Study 020 confirmed the strong intestinal absorptive effect, leading to a decrease in PN/IV volume of 4.4 L/week after 24 weeks of treatment, more than 2 L/week over placebo, with the potential for further reductions in the long-term extension studies including complete weaning of PN/IV support. No identifiable predictors of response were found based on assessments including age, gender, length of residual bowel, colon in continuity, baseline PN/IV requirements, and underlying etiology. Weekly PN/IV therapy was reduced by ≥1 or more days in over half of subjects, and by 3 or more days in over 20% of subjects after 1 year of GATTEX treatment. Long-term experience shows a clinical response of almost 75% at 1 year, and 10 subjects treated with GATTEX 0.05 mg/kg/day completely weaned from PN/IV. These 10 had been on PN/IV between 2 to 25 years. They were weaned from PN/IV as early as 3 months and as late as 27 months after initiation of GATTEX.

GATTEX associated AEs were mainly of GI origin and are consistent with its pharmacodynamic effect. The concern of GATTEX to increase growth of neoplasms in the intestine is being addressed by the label, communication to prescribers as described in the GATTEX REMS program, education of prescribers and by collecting additional data on these adverse events in the SBS registry.

In summary, the targeted intestinal effects of GATTEX offer SBS patients the first long-term treatment and next step in intestinal rehabilitation beyond supportive care. GATTEX improves intestinal function and increases absorption of nutrients and fluids, allowing for reduction in PN/IV fluid support with the possibility of permanently terminating PN/IV therapy.

1.0 Introduction

NPS Pharmaceuticals (hereafter NPS) is seeking US approval to market GATTEX® (teduglutide [rDNA]) powder for subcutaneous (SC) injection (GATTEX) for treatment of adult patients with Short Bowel Syndrome (SBS). GATTEX is a glucagon-like peptide 2 (GLP 2) that improves intestinal fluid and nutrient absorption in patients with SBS. GATTEX has received marketing authorization in Europe, but has not yet been marketed in any country.

The prevalence of adult SBS patients who require chronic PN/IV therapy in the United States (US) is approximately 10,000 to 15,000 (Oley Foundation for Home Parenteral and Enteral Nutrition Registry, 1992 and the American Society for Parenteral and Enteral Nutrition) SBS is associated with significant increases in mortality and morbidity. If approved in the US, GATTEX would be the first available agent for long-term use in SBS that directly increases the function of remaining intestine, thereby increasing absorption of fluids and nutrients. This increase in absorption allows for decreased PN/IV volume support and additional days off, for some eliminating the need for parenteral PN/IV therapy.

NPS designed the GATTEX development program to affirm a clinically significant effect on intestinal rehabilitation in SBS patients. One challenging aspect in studying changes in intestinal function and absorptive capacity in SBS patients is how to measure improvement. Clinically, the extent of absorption corresponds to the difference between fluid intake (oral + PN/IV) and output (urinary and fecal/stomal). Therefore, in the clinical studies this relationship was used to define any change in absorptive capacity. Two expert clinical panels in SBS concluded that at least a 20% reduction in PN/IV therapy (about 1 day reduction per week) would be clinically significant, establishing the responder definition used in the two 24-week, double-blind, placebo-controlled phase 3 studies.

The development program also included nonclinical safety and pharmacodynamic studies, and an extensive clinical pharmacology program. Both phase 3 studies included long-term open-label extensions.

This Briefing Document will summarize and review findings from the GATTEX development program, after first providing background information on SBS.

1.1 Unmet Medical Need in SBS

Short Bowel Syndrome (SBS) is caused by a reduction in intestinal absorptive capacity that typically follows partial or major surgical excision of the small intestine, with or without a colon resection. SBS can also occur secondary to congenital intestinal abnormality or underlying disease but most cases are caused by reduction in absorption secondary to surgery. SBS is a lifelong disease that is associated with significant increases in morbidity and mortality, particularly in patients who require chronic PN/IV therapy. In the US, there may be up to 10,000 to 15,000 adult SBS patients who require chronic PN/IV therapy, according to 1992 registry data from the Oley Foundation.

Because of the reduction in intestinal surface area, sub-optimized GI function occurs with reduced absorption of macronutrients, water, and electrolytes. The reduced absorption can lead to malnutrition, diarrhea, dehydration, and weight loss which highlight the clinical manifestations of SBS (Dudrick et al, 1991; O'Keefe et al, 2006; Nightingale, 1999; Rombeau and Rolandelli, 1987; Shanbhogue and Molenaar, 1994; Vanderhoof and Langnas, 1997; Wilmore et al, 1997; Scolapio et al, 1999). The extent of nutrition and fluid needs in SBS patients is dependent upon multiple factors including the amount of residual intestine and colon, presence of an ileal segment, and degree of spontaneous intestinal adaptation following resection.

Following surgically-induced SBS, some degree of intestinal adaptation is expected in patients. However, most patients require initial PN/IV support and many still require permanent PN/IV therapy. In SBS patients who are eventually weaned from chronic PN/IV therapy, most adaptation occurring in the remnant intestine resulting in increased

absorption and decreased GI fluid loss occurs within the first 6 months after surgery. However, a gradual adaptation may occur during and up to an additional 18 months. Spontaneous complete weaning of PN/IV is rare after six months and is unlikely to happen beyond 2 years. Thus, SBS patients who continue to require support beyond 2 years after the surgery causing SBS are unlikely to experience complete independence of parenteral nutrition and fluid support (Buchman, 1997). In a follow up study of SBS patients treated at a United Kingdom referral center, no patients were weaned from PN/IV therapy more than 5 years after the surgery that caused SBS (Lloyd et al, 2006).

Chronic PN/IV therapy is typically given 5-7 days a week for about 10 or more hours per day. While lifesaving in many SBS patients with intestinal failure, chronic PN/IV treatment is associated with increased morbidity and mortality (Messing et al, 1999; Scolapio et al, 1999).

Catheter-related infections at the insertion site or tunnel can lead to bacteremia and septicemia. Central venous thrombosis and/or thromboembolism are also significant risks associated with chronic PN/IV therapy (Buchman et al, 2003; DeLegge et al, 2007; Jackson and Buchman, 2005; Jeppesen, 2006). Liver disease (and eventual liver failure) is common among SBS patients being treated with PN/IV, more so than in many other patient types on parenteral nutrition (Cavicchi et al, 2000). Liver disease is one of the main causes of death in patients with permanent intestinal failure. In a prospective cohort study, the prevalence of liver disease among patients receiving home parenteral nutrition for permanent intestinal failure was 26% at 2 years, 39% at 4 years, 50% at 6 years, and 53% at 8 years. See Section 1.2 for more in depth discussion of the morbidity and mortality associated with SBS.

Intestinal transplant and bowel-lengthening surgery are the only effective treatments that can potentially restore absorptive capacity. Both procedures are associated with significant morbidity and mortality, restricting their use (Mardini et al, 2008). Intestinal transplantation is limited to patients who have developed life-threatening complications attributable to their intestinal failure and/or long-term use of PN/IV therapy

(DeLegge et al, 2007). Problems associated with small bowel transplantation include the need for lifelong immunosuppression and risk for intestinal rejection and lymphoproliferative disease. In addition, the risks of intestinal stricture and small bowel obstruction increase with repeated surgical interventions.

Given the risk of long-term PN/IV therapy, the therapeutic ideal is to optimize intestinal function while attempting to wean patients from parenteral support. The current treatment strategy is to promote intestinal rehabilitation with mostly a combination of specialized diets, anti-diarrheal, anti-secretory agents, and parenteral nutrition/IV fluids to meet the needs of SBS patients. To date, there is no targeted long-term treatment aimed at optimizing remnant intestinal capacity to increase absorption of fluids and nutrients and decrease intestinal fluid and nutrient loss. For SBS patients on chronic PN/IV therapy in intestinal rehabilitation, the therapeutic goal is to decrease the need for PN/IV and ideally wean patients completely off PN/IV therapy, while promoting enteral feeding and maintaining clinical status. Increasing the time off from PN/IV therapy may decrease the burden of illness suffered by SBS patients.

Suboptimal treatment of SBS can ultimately lead to severe malnutrition, impaired cardiac, hepatic, and renal functions, fluid retention, intestinal mucosa atrophy, loss of intracellular minerals (zinc, magnesium, and phosphorus), osteoporosis, diminished cell-mediated immune function, increased risk of infections, and eventually death. Thus, clinical care of SBS patients has focused on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, and anti-diarrheal and anti-secretory agents.

Currently two products, ZORBTIVE® (somatropin [rDNA origin] for injection) and NUTRESTORE™ (L glutamine powder for oral solution) are approved for the treatment of SBS for up to 4 and 16 weeks, respectively, in the US. Thus both treatments are intended for short-term use. ZORBTIVE is indicated for the treatment of SBS in patients receiving specialized nutritional support. NUTRESTORE is indicated for the treatment of SBS in patients receiving specialized nutritional support when used in conjunction

with a recombinant human growth hormone that is approved for this indication. Specifically, glutamine and recombinant human growth hormone therapy should be used in conjunction with optimal management of SBS for up to 4 weeks, followed by continued NUTRESTORE for up to 16 weeks (see NUTRESTORE US Package Insert).

In summary, while the ideal therapeutic goal is to optimize intestinal function and to reduce and hopefully wean patients from long term PN/IV therapy, there are no long-term treatment options that improve intestinal function and facilitate intestinal rehabilitation. Surgical treatment including transplantation is the only option for long-term intervention and it is restricted to a subset of patients because of significant surgically related morbidity and mortality. There are no approved pharmacological treatments for SBS that increase the capacity of the remaining bowel mucosa to absorb fluids and nutrients on a long-term basis.

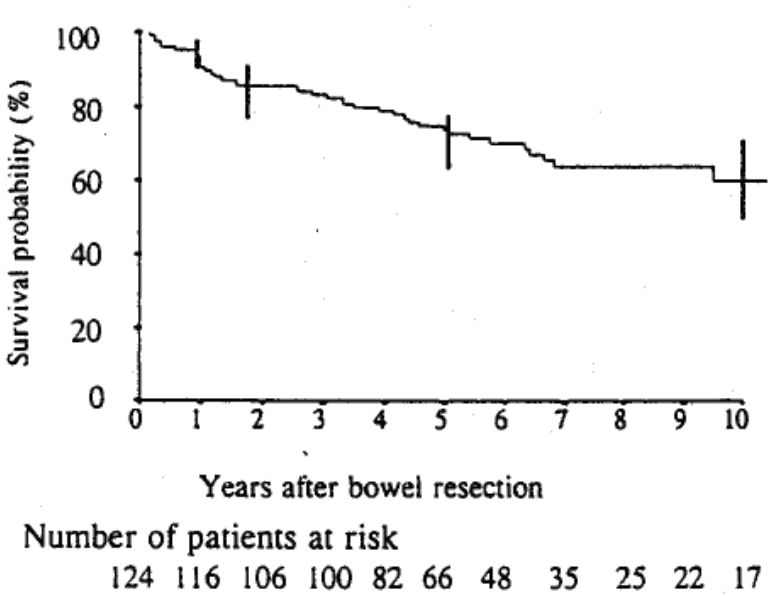
NPS developed GATTEX to fulfill the unmet need for a long-term treatment that could increase intestinal function leading to increased absorption of fluids and nutrients. Even a 1- to 2-day reduction in the amount of weekly PN/IV fluids could have significant benefit to SBS patients. A reduction in the burden of parenteral support may result in clinically meaningful benefits such as an increase in the number of days off of PN/IV support per week, decreased nocturia and less interrupted sleep, reduced infusion time per day, and reduced costs and resources associated with managing patients dependent on PN/IV support.

1.2 SBS and Chronic PN/IV Associated with Significant Morbidity and Mortality

SBS is directly associated with significant morbidity and mortality. Potential morbidity that is attributable to SBS includes gastric hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhea, diarrhea, small bowel bacterial overgrowth, and weight loss (Hollwarth 1999; Nightingale and Woodward, 2006; O'Keefe et al, 2006). The increased mortality in SBS patients is directly related to the length of

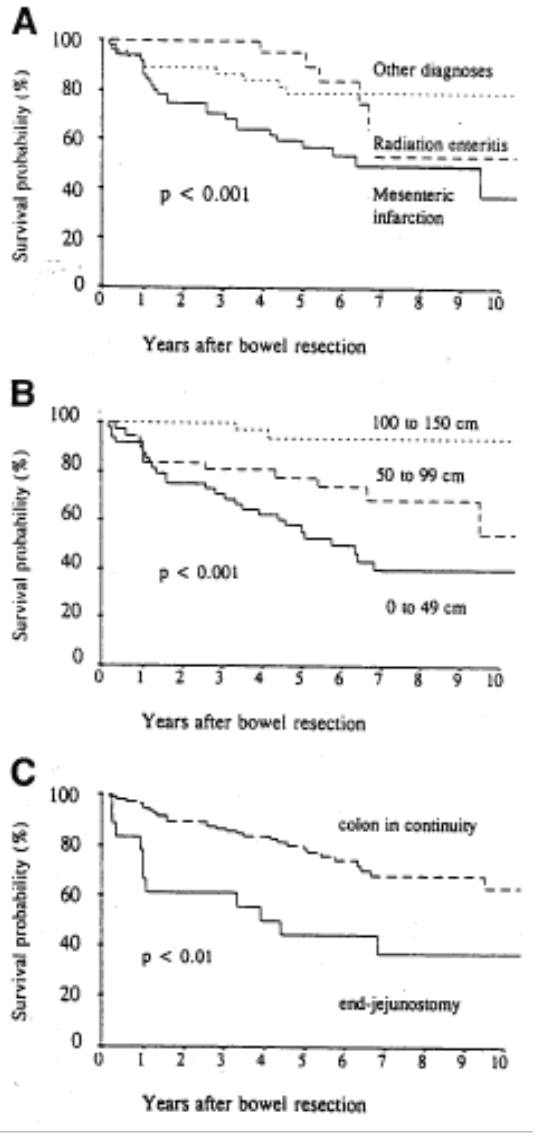
remaining bowel. Ten-year survival following bowel resection in non-malignant SBS patients is shown in Figure 8. Patients with bowel remnants of < 50 cm have greatly reduced survival (Figure 9).

Figure 8. Probability of Survival in 124 Adult Patients with Nonmalignant Short Bowel Syndrome



Note: Vertical bars indicate 95% confidence intervals (CI) at 1-, 2-, 5-, and 10-year follow-up. Survival probabilities were 94% (CI = 90 to 98), 86% (CI = 80 to 92), 75% (CI = 67 to 83), and 60% (CI = 49 to 71) at these intervals, respectively.
Source: Messing et al, 1999

Figure 9. Survival Rate of 124 Adult Patients with Nonmalignant SBS



CI = 95% confidence interval; SBS = shot bowel syndrome
Note: Significant factors were (A) main types of primary disease leading to small bowel resection; (B) postduodenal remnant small bowel length with 5-year survival rates of 93% (CI = 84 to 100), 79% (CI = 66 to 92), and 57% (CI = 43 to 71) for remnant lengths of 100 to 150 cm, 50 to 99 cm, and < 50 cm, respectively; and (C) presence (type 1) or absence (types 2 and 3) of end-jejunostomy, with 5-year survival rates of 44% (CI = 21 to 67) and 80% (72 to 88), respectively. Survival distributions were compared using the log rank test.
Source: Messing et al, 1999

Malignancy is a common cause of death among patients with SBS. Vantini and coworkers reported on the causes of death in 68 patients with intestinal failure (n=60 SBS, n=8 chronic idiopathic intestinal pseudo-obstruction) (Vantini et al, 2004). Over a median follow-up period of 36 months, 22 patients died, 4 from new malignances (Vantini et al, 2004). In a prospective study of 228 patients with SBS in Europe with a median PN duration of 7 years, 10 incident malignancies were diagnosed (Van Gossum et al, 2001).

Chronic PN/IV therapy is also associated with increased morbidity and mortality in many populations including SBS (Messing et al, 1999; Scolapio et al, 1999). Insertion site, tunnel, and catheter-related blood stream infections may lead to bacteremia and septicemia, central venous thrombosis, and even embolism (Buchman et al, 2003). Other potentially life-threatening complications from PN/IV include venous thromboembolism and fulminant hepatic failure (DeLegge et al, 2007; Jackson and Buchman, 2005; Jeppesen, 2006). In addition, significant morbidity includes parenteral nutrition-associated liver disease (PNALD) and irreversible liver damage (Tazuke and Teitelbaum, 2009).

Because of the risks with chronic PN/IV, the American Gastroenterological Association Medical Position Statement on SBS recommends that a potential treatment option for PNALD should attempt to reduce the toxic exposure to parenteral nutrition constituents administered to patients (American Gastroenterological Association, 2003). In SBS, the current treatment strategy is to promote intestinal rehabilitation by optimizing remnant intestinal capacity to increase intestinal absorption of fluids and nutrients and decrease intestinal fluid loss to decrease the need for PN/IV and ultimately wean patients completely off PN/IV therapy.

2.0 Description of GATTEX

2.1 GLP-2

Human glucagon-like peptide-2 (GLP-2) is a 33-amino acid proglucagon-derived peptide that facilitates efficient digestion and absorption of nutrients. GLP-2 is mainly responsible for the maintenance and expansion of the gastrointestinal (GI) mucosal surface area through the regulation of proliferation and apoptosis of the intestinal epithelium (Drucker et al, 1996; Tsai et al, 1997). Furthermore, GLP-2 promotes energy absorption through a number of mechanisms including enhanced capacity for carbohydrate, amino acid, and lipid absorption, increased activity and expression of brush border digestive enzymes, and increased mucosal hexose and nutrient transport via upregulation of glucose transporter 2 (GLUT2) and the sodium-dependent glucose transporter (SGLT1). In addition, GLP-2 enhances mucosal barrier function, and acutely increases intestinal and portal blood flow (Wojdemann et al, 1998; Wojdemann et al, 1999; Benjamin et al, 2000; Guan et al, 2003; Stephens et al, 2006; Meier et al, 2006; Cheeseman & Tsang, 1996; Cheeseman, 1997; Cottrell et al, 2006; Bremholm et al, 2009).

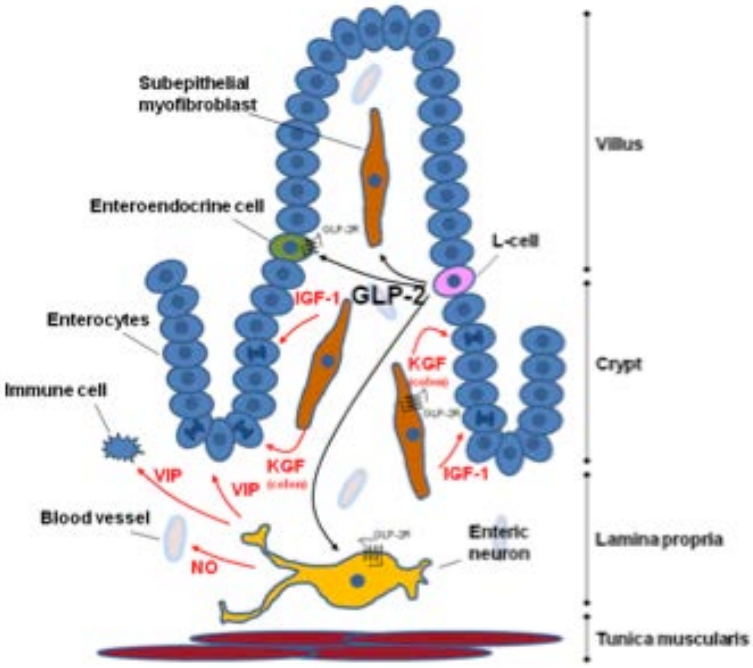
Native GLP-2 is secreted in response to luminal nutrients by endocrine L-cells, which are primarily located in the distal intestinal tract, an area often resected in SBS patients (Xiao et al, 1999; Estall & Drucker, 2006). The secretion profile for GLP-2 is biphasic, with an early peak 30 minutes following nutrient ingestion and a more prolonged peak at 60 to 120 minutes (Drozdowski and Thomson, 2009). The biological half-life of circulating GLP-2 is relatively short (approximately 7 minutes in humans) due to rapid degradation by the proteolytic enzyme dipeptidyl peptidase (DPP-IV) and extensive renal clearance (Hartmann et al, 2000; Tavares et al, 2000). The biological actions of GLP-2 may be further limited by competition at the GLP-2 receptor with its own main metabolite, GLP-2 (3-33), that is produced as a result of DPP-IV cleavage.

The effects of native GLP-2 (and GATTEX) are mediated by the GLP-2 GLP-2R, which is highly specific to GLP-2, and does not increase cAMP production by related glucagon

peptide family members (Munroe et al, 1999; DaCambra et al, 2000). The specificity of GLP-2 activity is partly attributed to the discrete localization of the GLP-2R receptor. Within the GI tract, GLP-2R receptor protein expression has been reported in subpopulations of enteroendocrine cells, and intestinal subepithelial myofibroblasts (Yusta et al, 2000; Guan et al, 2006; Orskov et al, 2005). In addition, GLP-2R receptor expression has been demonstrated in enteric neurons of the submucosal and myenteric plexus in the small and large intestine (Bjerknes & Cheng, 2001; Guan et al, 2006; Nelson et al, 2007).

The effects on intestinal physiology initiated by the GLP-2R are diverse and therefore involve multiple indirect mechanisms and factors (Figure 10). These mediators likely interact in a complementary fashion to affect different intestinal responses. Insulin-like growth factor (IGF)-1, keratinocyte growth factor (KGF), the erbB signaling network, nitric oxide (NO) and vasoactive intestinal polypeptide (VIP) have been implicated in GLP-2-induced intestinal growth, blood flow and prevention of intestinal damage (Orskov et al, 2005; Yusta et al, 2009; Guan et al, 2003; Guan et al, 2006; Sigalet et al, 2007). Neural GLP-2R receptor signaling may also influence the crypt epithelium and gastrointestinal motility (Bjerknes and Cheng, 2001).

Figure 10. Expression of the GLP-2R in Intestinal Endocrine Cells, Intestinal Subepithelial Myofibroblasts, and Enteric Neurons Suggests that GLP-2, Released From L-Cells, Acts Indirectly to Produce Diverse Actions in the Intestine



Based on Dubé & Brubaker, 2007.

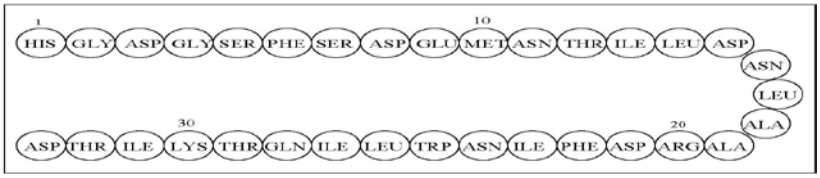
2.2 Overview of GATTEX

GATTEX (teduglutide [rDNA origin]) is a 33 amino acid GLP-2 analog, which is manufactured using a strain of *Escherichia coli* modified by recombinant DNA.

The schematic diagram for teduglutide (GATTEX) is displayed in Figure 11. Teduglutide is designated chemically as: L-histidyl-L-glycyl-L-aspartyl-L-glycyl-L-seryl-L-phenylalanyl-L-seryl-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-

isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-isoleucyl-L-glutaminyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid and its molecular weight is 3752 Daltons.

Figure 11. Schematic Diagram of Teduglutide



Teduglutide (GATTEX) differs from GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus, resulting in resistance to degradation by DPP-IV (Tavares et al, 2000), and therefore a longer elimination half-life ($t_{1/2}$) of approximately 2 hours and enhanced biological activity, compared to the half-life of 7 minutes for the native peptide. Similar to GLP-2, teduglutide promotes growth and repair of GI epithelium in models of disease (e.g., small bowel resection models), including enhanced adaptation and nutrient absorption following small bowel resection and alleviation of TPN-induced hypoplasia in rodents (refer to Section 3.0).

2.3 Regulatory History

NPS received the Food and Drug Administration's (FDA) guidance from the Division of Gastroenterology during the development program of GATTEX for SBS. Although there was not a Special Protocol Assessment done on the phase 3 study protocols, the key development meetings and regulatory actions are shown in Table 2.

Of note, the prevalence of PN/IV infusion-dependent SBS among adults residing in the US is estimated to be no more than approximately 15,000. Therefore, the estimated number of patients in the US that might benefit from treatment with GATTEX is well below the threshold to qualify for Orphan Drug Designation. Consequently, NPS submitted a request for Orphan Drug Designation (Application #99 1269) based upon an

indication for the treatment of SBS. The FDA Office of Orphan Products Development approved this request on 29 June 2000.

Table 2. Regulatory Milestones for GATTEX

Date	Milestone
20 October 1998	Pre-Investigational New Drug (IND) meeting conducted with Agency with the focus of discussing the planned toxicology and phase 2 program.
26 April 1999	IND 58,213 filed.
29 June 2000	Agency granted Orphan Drug Designation for GATTEX in treatment of SBS
06 October 2003 – End of phase 2 Meeting	Agency discussed the following key elements of the Study 004 protocol: • primary endpoint – patients achieving a reduction of 20% to 100% from baseline in weekly PN/IV volume at Week 24 • selection of the SBS patient population • PN/IV volume optimization/stabilization procedure • use of placebo as the control • GATTEX 0.05 mg/kg/day and 0.10 mg/kg/day dose levels to be tested • statistical analysis methods
19 December 2003	Follow-up nonclinical discussion.
06 June 2006	Agency provided pharmacokinetic (PK) advice, including: design of studies in subjects with renal impairment (Study 018) and in subjects with hepatic impairment (Study 017). No formal drug-drug interaction studies would be required. NDA should include analyses to determine the effect of age, gender, and race on the PK of GATTEX.
23 January 2007	Agency provided clinical advice on the planned change from a dichotomous to categorical primary efficacy endpoint, noting that if the study were positive for new end point but negative for the original endpoint it would be a review issue.
18 January 2008 – Type C Meeting	Agency acknowledged that Study 004 showed clinical benefit, albeit not a dose response. Despite the statistical result of Study 004, the Agency clarified that only 1 additional study was needed (a confirmatory 2-arm design of GATTEX 0.05 mg/kg/day vs. placebo) to support an NDA. The monitoring of immunogenicity over the study period was discussed. FDA advised that a thorough QT study should be conducted (i.e., Study C09-001).

Table 2. Regulatory Milestones for GATTEX (Continued)

Date	Milestone
14 July 2008	Further discussions with Agency regarding the results of Study 004: The Agency re-confirmed that an additional study (i.e., 020) would need to be completed prior to NDA filing. It was discussed that the "original" endpoint (i.e., a reduction of 20% to 100% from baseline in PN/IV volume at Week 20 and at Week 24) would be used in the upcoming study, with an alpha control of 0.05. The Agency also encouraged collection of neutralizing antibody data in the additional study. FDA also reaffirmed the need for a Segment III pre- and post-natal development study in rats prior to filing.
25 April 2011 – Pre-NDA Meeting	Meeting objectives included the discussion of the content and format of the NDA filing (clinical/ nonclinical/logistics). Priority Review status was introduced by NPS and remained a review issue at the close of the meeting. Subsequently the NDA received a standard review designation.
30 November 2011	NDA filed.
29 March 2012	NDA Amendment submission of 4 month safety update `
10 August 2012	PDUFA date extended to 30 December 2012 based on solicited major amendment submission

A marketing authorization application was submitted by the Danish company Nycomed (now a Takeda company) for teduglutide in Europe with the brand name Revestive on March 3, 2011 through the centralized procedure. Review of the application proceeded with only one extension of the clock requested by Nycomed throughout the review cycle. Following a Committee for Medicinal Products for Human Use (CHMP) request, an ad hoc expert group meeting was convened on May 8, 2012 to provide advice on the list of questions adopted by the CHMP at its March 2012 meeting. As noted in the Scientific Advisory Group minutes, which were issued May 16, 2012, three representatives from FDA participated by telephone (during the closed session). The CHMP issued a positive opinion for granting Marketing Authorization on June 21, 2012 and the Commission adopted this decision on August 30, 2012 granting marketing authorization under Regulation (EC) No. 726/2004 of the European Parliament and of the Council for "Revestive - teduglutide", as an orphan medicinal product for human use.

2.4 Proposed Indication, Dose and Administration

GATTEX® (teduglutide [rDNA origin]) is indicated for the treatment of adult patients with SBS to improve their intestinal absorption of fluid and nutrients.

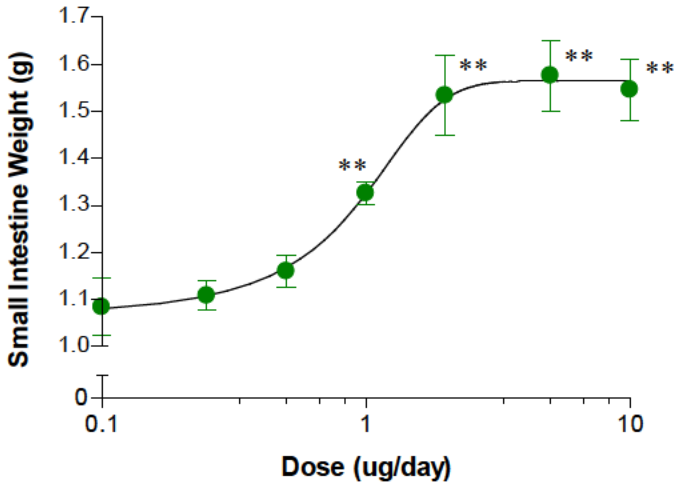
The recommended dose of GATTEX is 0.05 mg/kg of body weight, administered once daily by SC injection. The injection site should be alternated between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. The dose should be reduced by 50% for patients with moderate or severe renal impairment and for those with end-stage renal disease.

3.0 Nonclinical Overview

Teduglutide has shown primary pharmacodynamic activity in mice, rats, rabbits, ferrets, dogs, minipigs, and cynomolgus monkeys. Nonclinical data consistent with the clinical data (Section 7.3.1) have been observed with teduglutide.

The intestinotrophic activity of teduglutide was studied in healthy animals through measures of intestinal weight, morphological analysis, and in some cases protein and DNA content, barrier function, and D-xylose absorption. The intestinotrophic effect was used to elaborate a full pharmacological profile of teduglutide, including an assessment of dose response, optimal treatment regimen, maximum effect, and reversibility. Teduglutide showed intestinotrophic activity in mice, rats, ferrets, dogs, and monkeys. The intestinotrophic effect follows a sigmoidal dose-response curve with a median effective dose of 0.98 µg/day in mice (equivalent to 0.05 mg/kg/day in humans). Depending on dose and duration of treatment, the intestinotrophic effect reaches a plateau, and rapidly reverses if administration is discontinued. Daily teduglutide administration for 14 days did not result in a reduction of activity over time (Figure 12) or changes in body weight, and the intestinotrophic effect in mice was independent of a once or twice daily treatment regimen.

Figure 12. Increase in Small Intestinal Weight with Teduglutide



** p < 0.01 compared to the vehicle control group

Pharmacology studies on the intestinotrophic activity of teduglutide in healthy animals were complemented by studies in various intestinal disease that comprise animal models of TPN-induced intestinal hypoplasia, short bowel resection, and various models of induced and spontaneous GI damage and dysfunction dysfunction. Similar to GLP-2, teduglutide promotes growth and repair of GI epithelium, including expansion of mucosal surface area, enhanced adaptation and absorptive capacity following small bowel resection and alleviation of TPN-induced hypoplasia in rodents (Scott et al, 1998, Martin and Sigalet 2000). Teduglutide has shown beneficial effects in several nonclinical studies by a decrease in mortality and improvement of disease-related histopathology in murine models of intestinal damage such as indomethacin-induced enteritis, dextran sulfate-induced colitis, and chemotherapy-induced mucositis (Boushey et al, 1999; Drucker et al, 1999; Boushey et al, 2001; Tavakkolizadeh et al, 2000). Teduglutide also diminished intestinal pathophysiology by reducing intestinal permeability, luminal uptake, and intestinal allergy-induced and stress-induced inflammation (Cameron et al, 2003; Cameron et al, 2005).

No extra-intestinal pharmacodynamic effects are expected for GATTEX due to its specificity for the GLP-2R receptors in the gastrointestinal tract. Increases in food intake and body weight might occur and are considered contributing beneficial effects relative to the clinical indication. Although GLP-2R mRNA has been found reported in a few extra-intestinal localizations, specifically the endocrine pancreas, heart, cervix, lung, and brain, animal studies did not reveal any pharmacodynamic or adverse clinical impact in these organs.

Repeat-dose toxicity studies were conducted in CD-1 mice (up to 26-weeks) and in Cynomolgus monkeys (up to 52-weeks). Mice and monkeys were chosen because both have demonstrated the expected intestinotrophic effect upon teduglutide administration. The pattern of toxicity was consistent amongst the various species studied, with the majority of the findings being associated with the pharmacodynamic action of teduglutide: Hypertrophy and hyperplasia of the intestinal mucosa and increases of food consumption and body weight were observed compared to control. Effects on intestinal mucosa were described as increased length of intestinal villi and enlarged crypts. The exaggerated pharmacodynamic activity of teduglutide included a stimulation of cell proliferation, which gave rise to hyperplasia of bile- and pancreatic duct epithelium. These findings either partially or completely resolved during the recovery period. The hyperplasia was observed in mice and monkeys above clinically relevant exposures.

A cardiovascular and respiratory safety pharmacology study was conducted in beagle dogs, and no treatment-related effects were observed that were attributed to teduglutide. No effect of teduglutide was noted on the human ether-à-go-go-related gene channel or canine cardiac Purkinje fibers. In addition, no central nervous system effects were observed in rodents receiving teduglutide at doses well above the targeted clinical therapeutic dose.

The genotoxic potential of teduglutide was evaluated in 3 studies. Teduglutide did not induce mutagenic changes in the bacterial reverse mutation assay (Ames assay) or in a

mammalian (mouse) erythrocyte micronucleus test, nor was it clastogenic in the Chinese hamster ovary cell chromosome aberration assay.

In a 2-year carcinogenicity study in the Wistar Han IGS rat, the survival of both male and female treated groups was comparable to that of the control groups. Statistically significant treatment-related neoplastic changes included benign tumors of the bile duct epithelium seen in male rats treated at 35 mg/kg/d (at an incidence of 5/50) and adenomas of the jejunal mucosa seen in 5/50 males treated at 35 mg/kg/d. The No Observable Effect Level (NOEL) for benign neoplastic changes associated with teduglutide treatment was considered to be 3 mg/kg/day, yielding a systemic exposure of 2.3 µg•hr/mL, which is 9.8 times the human exposure at the recommended dose of 0.05 mg/kg/day. No treatment-related malignant tumors were observed following treatment with teduglutide in this rat carcinogenicity study.

Preliminary results of the 2-year carcinogenicity study in Crl:CD1 (ICR) mice did not show a statistically significant change in survival in either sex.

Adenocarcinoma in the jejunum had a significant positive trend ($p = 0.0155$), although none of the treated groups had a significant increase in this case ($p = 0.1084$ at 12.5 mg/kg/day). The positive trend in jejunal adenocarcinoma was due to a nonsignificant increase at 12.5 mg/kg/day in the males (Table 3). The 12.5 mg/kg/day dose resulted in an exposure level 150 (AUC) and 480 (C_{max}) times the recommended human dose of 0.05 mg/kg/day.

Table 3. Selected Microscopic Observations in the Jejunum of Mice

Sex	Male				Female			
Dose Level (mg/kg/day)	**0**	**1.0**	**3.5**	**12.5**	**0**	**1.0**	**3.5**	**12.5**
Jejunum								
Number examined	68	69	73	68	69	69	68	69
Villus, Increased Length								
Minimal	0	21	22	11	0	11	15	7
Slight	0	0	2	1	0	0	3	3
Hyperplasia, Mucosa								
Minimal	0	8	5	3	2	4	9	12
Slight	1	0	0	0	0	0	2	1
Adenocarcinoma								
Present	0	1	0	4	0	0	0	1

The absence of adenoma in the jejunum of males suggests no biological continuity between the mechanistically-induced hyperplasia (generally minimal at all dose levels) and the occurrence of adenocarcinoma. However, this is a rare tumor in Crl:CD1 (ICR) mice and therefore the occurrence in the high-dose males may be test article related.

The effect of GLP-2 and analogs has been investigated in a well-known mouse model of colon carcinogenesis (Thulesen et al., 2004; Iakoubov et al., 2009). Although a synthetic Gly-GLP-2 (same or similar amino acid sequence as teduglutide, but different manufacturing process) was used, these studies are considered relevant to a carcinogenic risk assessment of GATTEX. Prolonged treatment with Gly-GLP-2 promoted (i.e., accelerated) growth of tissue with existing cancer or tissue that was exposed to known carcinogens in the mouse intestine. However, these findings are in contrast to other studies. Specifically, a xenographic cancer transplant study was conducted. Koehler *et al*. examined the effects of exogenous native GLP-2(1-34) on proliferation and survival

of colon cancer cells *in vitro* and in human colon xenografts implanted in nude mice (Koehler et al, 2008). Chronic exogenous native GLP-2(1-34) administration did not significantly increase the weight, number, or growth of the intestinal tumor xenografts.

Reproductive and developmental toxicity studies evaluating SC administration of teduglutide have been carried out in rats and rabbits at doses up to 50 mg/kg/day. Teduglutide was not associated with effects on reproductive performance, *in utero* or developmental parameters measured in studies to investigate fertility, embryo-fetal development in the rat and rabbit, and pre- and post-natal development in rats.

4.0 Overview of Clinical Pharmacology

4.1 Mechanism of Action

Teduglutide (GATTEX) is an analog of naturally occurring human GLP-2, a peptide secreted by L-cells of the distal intestine. GATTEX binds to the GLP-2R receptors located in intestinal subpopulations of enteroendocrine cells, subepithelial myofibroblasts and enteric neurons of the submucosal and myenteric plexus. Activation of these receptors results in the local release of intestinal mediators.

4.2 Pharmacokinetics

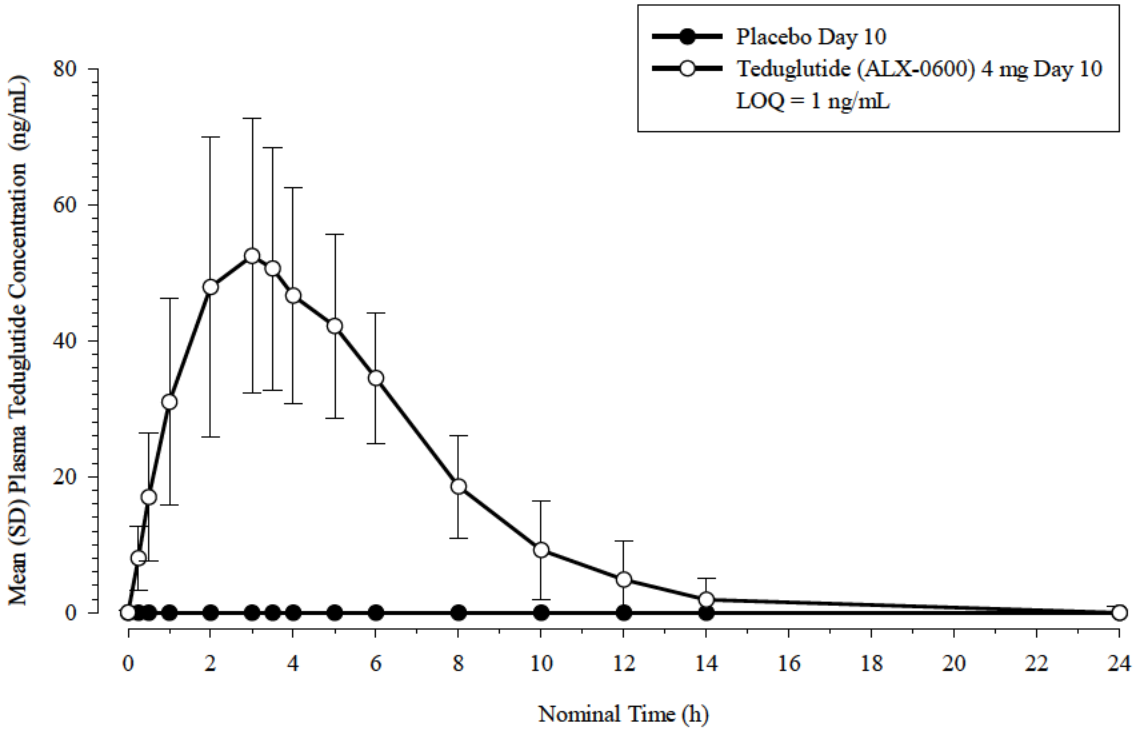
4.2.1 Absorption

In a phase 1, randomized clinical study of healthy subjects (CL0600-006; hereafter referred to as Study 006), the mean bioavailability of 0.12 mg/kg GATTEX was 87% after a single SC injection relative to intravenous (IV) infusion. GATTEX was rapidly absorbed and eliminated from plasma following SC injection (mean half-life [t½] = 2.23 hours). These findings were confirmed in a second phase 1 study in healthy subjects (CL0600-015; hereafter referred to as Study 015), which was conducted to investigate the suitability of once-daily SC injection in the arm, thigh, and abdomen. The results of Study 015 indicate that SC administration of GATTEX in the abdomen, arm, and thigh result in similar exposures.

GATTEX was rapidly absorbed from SC injection sites, with maximum plasma levels occurring approximately 3-5 hours after dose administration at all dose levels. The absorption of GATTEX is dose proportional at single and repeated SC doses up to 50 mg (Study CL0600-022; hereafter referred to as Study 022). Following SC administration of a 0.05 mg/kg dose of GATTEX to subjects with SBS (Study CL0060-004; hereafter referred to as Study 004), mean peak GATTEX concentration (C_{max}) was 36 ng/mL and overall mean area under the curve ($AUC_{0\text{-}inf}$) was 0.235 µg•hr/mL. The absolute bioavailability of SC GATTEX is high (88%). No accumulation of GATTEX is observed

following repeated SC administration (e.g., plasma teduglutide concentration vs. time profile on Day 10 after 10 consecutive days of GATTEX dosing shown in Figure 13).

Figure 13. Mean (± SD) Plasma Teduglutide Concentrations on Day 10 – Study C10-003



SD = Standard deviation
Note: Study medication administered at hour 0.
Source: Study C10-003 CSR, Figure 11-8

4.2.2 Distribution

Following IV administration in healthy subjects, GATTEX is not widely distributed throughout the body and is primarily retained in the intravascular compartment (i.e., volume of distribution = 103 mL/kg, similar to blood volume).

4.2.3 Metabolism

As a peptide, GATTEX is not metabolized by common drug metabolizing enzymes (e.g., cytochrome P450 [CYP], uridine diphosphate glucuronyltransferase, glutathione S-transferase). Instead, it is likely to be metabolized by hydrolytic degradation like native GLP-2 (i.e., removed from the circulation by the kidney through a mechanism involving both glomerular filtration and tubular catabolism [Tavares et al, 2000]). Studies investigating GATTEX inhibition or induction of human CYP-450 enzymes or inhibitor potential and *in vitro* stability in human hepatocytes support a lack of metabolism by pathways associated with hepatocytes. No abnormal accumulation of GATTEX was observed when administered to individuals with moderate hepatic impairment (Study CL0600-017; hereafter referred to as Study 017) (refer to Section 4.2.5.1).

4.2.4 Excretion

Following IV administration, GATTEX plasma clearance was 123 mL/hr/kg (similar to glomerular filtration rate) (Study 006), suggesting that GATTEX is primarily eliminated by the kidneys. In subjects with moderate or severe renal impairment or end-stage renal disease, systemic exposure to GATTEX increased with increasing degree of renal impairment (Study CL0600-018; hereafter referred to as Study 018).

4.2.5 Pharmacokinetics in Special Populations

The pharmacokinetics of GATTEX in various subgroups was examined in an overall population pharmacokinetic analysis, which was performed using all available pharmacokinetic data from 11 completed clinical studies. None of the covariates of age, gender, race and dosing occasion had a significant effect on the pharmacokinetics of GATTEX. Similar pharmacokinetics results were observed in healthy subjects and subjects with SBS or Crohn's disease. In addition, concentration-time profiles of GATTEX plasma concentrations were similar for healthy non-elderly and elderly subjects (Study 018); pharmacokinetic characteristics were not markedly different.

4.2.5.1 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of GATTEX following SC administration of 20 mg GATTEX was investigated in a phase 1 study in patients with mild and moderate hepatic impairment (Study 017). The maximum exposure and the overall extent of exposure to GATTEX following single 20 mg SC doses were lower (10 to 15%) in subjects with moderate hepatic impairment relative to those in healthy matched controls, which was not considered clinically significant.

4.2.5.2 Renal Impairment

The effect of renal impairment on the pharmacokinetics of GATTEX following SC administration of GATTEX 10 mg was investigated in a phase 1 study. With progressive renal impairment up to end-stage renal disease the primary pharmacokinetic parameters of GATTEX increased up to a factor of 2.6 (AUC_{inf}) and 2.1 (C_{max}) compared to healthy subjects.

4.2.5.3 Elderly Patients

In a phase 1 study no difference in pharmacokinetics of GATTEX could be detected between healthy subjects younger than 65 years versus those older than 65 years (Study 018). Experience in subjects 75 years and above is limited.

4.3 Pharmacodynamics

Like GLP-2, GATTEX is 33 amino acids in length, but with an amino acid substitution of alanine by glycine at the second position of the N-terminus of GLP-2. The single amino acid substitution, relative to naturally occurring GLP-2, results in resistance to *in vivo* degradation by DPP-IV.

Gastrointestinal Absorption

The extent of malnutrition suffered by the SBS patient is largely dependent upon the extent of residual small intestine, presence of colon with the ileocecal valve, and the

degree of adaptation following resection. Intestinal adaptation involves increases in crypt depth and villus height as well as accelerated mucosal proliferation that partially compensates for loss of the resected bowel. Despite adaptation, a large proportion of SBS patients require the use of PN/IV to supplement and stabilize their nutritional needs. Given drawbacks of PN/IV, increasing the absorptive capacity of the remaining intestine in order to decrease either the intensity or duration, or obviate the SBS patient's dependence on PN/IV, is a rational therapeutic goal.

Increased capacity to absorb fluids and nutrients with GATTEX, as observed in nonclinical studies (Drozdowski and Thomson, 2009; Estall and Drucker, 2006), is in line with the goals of intestinal rehabilitation for SBS patients, including optimization of remnant GI function for SBS as well as decreasing GI fluid losses and, when possible, minimizing exposure to PN/IV constituents. These effects were evaluated both nonclinically and in clinical pharmacology Study ALX-0600-92001 (hereafter referred to as Study 92001) in humans. Specifically, aspects of evaluation included: intestinal surface using direct biopsy data; nutrient and energy absorption using stool balance studies; GI fluid losses measured by changes in fecal/stomal output; and absolute fluid absorption based on changes in intake-output measurements on a standardized diet.

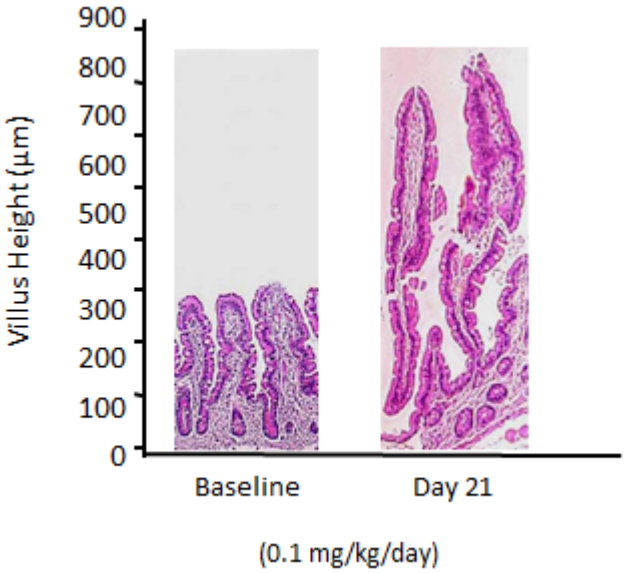
The pharmacodynamics effects of GATTEX on intestinal structure and function were investigated in Study 92001, which enrolled 17 adult subjects with stable SBS due to various underlying etiologies and having various residual anatomies, using ascending doses of 0.03, 0.10, and 0.15 mg/kg once daily.

The subjects were treated with GATTEX for 21 days and were then followed for 21 days off treatment. During 3 admissions to a metabolic research unit – at baseline, end-of-treatment, and end of follow-up – over the 6-week study period, 72-hour nutrient absorption studies were performed to evaluate effects of GATTEX administration on absolute and relative absorption as well as stomal or fecal output of fat, nitrogen, sodium, potassium, calories, and GI fluid. Endoscopies were performed to obtain intestinal biopsy samples for histopathological examination. The protocol mandated that subjects have no

change in their PN/IV volume requirements and have individualized diets to keep caloric intake constant during these 72-hour admissions so that changes in fecal wet weight and/or urinary output would indicate changes in absorption.

Enhanced key structural adaptation in the intestinal mucosa (i.e., increased jejunal villus height and crypt depth, as observed on biopsy samples) was observed after 21 days of GATTEX treatment (illustrative results for 1 subject shown in Figure 14).

Figure 14. Increased Intestinal Villus Height and Crypt Depth in SBS Subject Treated with GATTEX (Study 92001)



Absorption of important macronutrients and electrolytes improved during GATTEX treatment, with corresponding decreases in their excretion in fecal and stomal fluid. GATTEX increased absolute GI fluid absorption by almost 900 mL per day (Table 4) and decreased GI fluid losses (fecal or ostomy output) by approximately the same amount (Table 5) (each $p<0.001$ vs. baseline), representing approximately a 30% reduction in fecal losses in these SBS subjects. Increased fluid absorption led to significantly increased urine volume (+508 mL/24 hours, $p<0.001$).

Table 4. Change from Baseline in Mean Absolute Absorption of Nutrients, Energy, and GI Fluids (Study 92001)

Change in:	Fat (g/day)	Nitrogen (g/day)	Sodium (g/day)	Potassium (g/day)	Calories (kcal/day)	GI Fluids (mL/24 h)
Mean Absolute Absorption†	11.2	2.0*	0.6	0.4*	203	892***
Fecal/Stomal Output	-11.5*	-1.7**	-0.6	-0.4**	-259**	

* p<0.05; ** p<0.01; ***p<0.001 vs. baseline.
† Measured based on wet weight obtained through stool balance studies using bomb calorimeters.
Note: Pooled data

Table 5. Mean Fecal/Stomal Output (Study 92001)

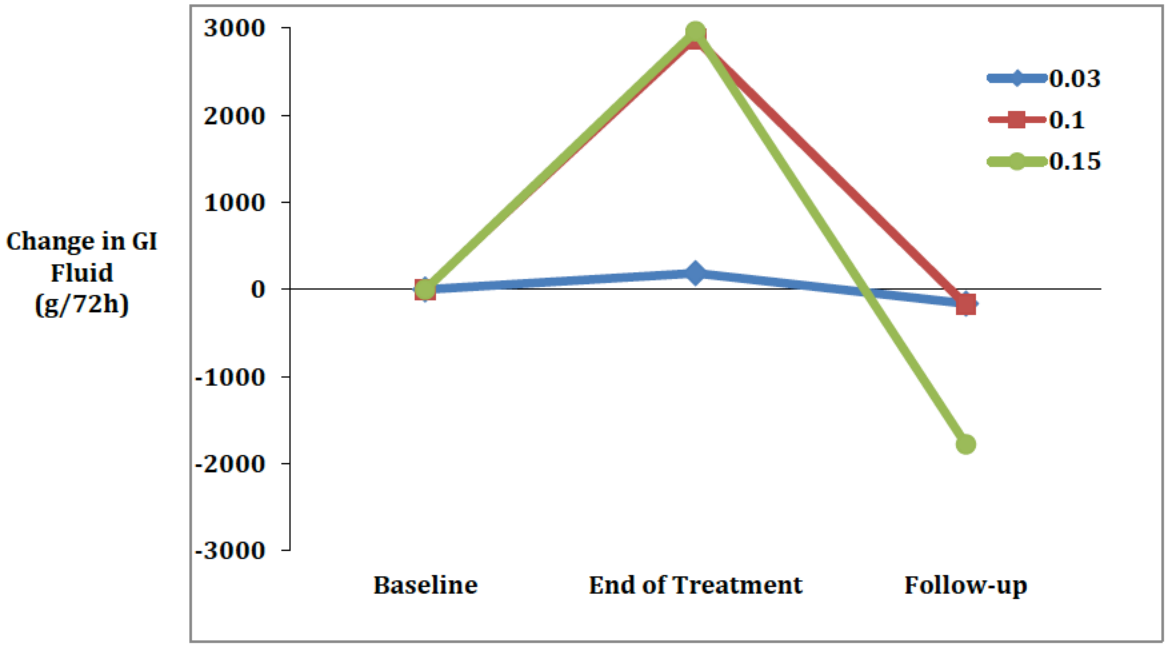
Baseline (mL/24 h)	End of Treatment (mL/24 h)	Change (mL/24 h)
2904.2	2017.5	-887***

***p<0.001 vs. baseline.
Note: Pooled data

Significant increases in fluid and nutrient absorption were observed in the 0.10 and 0.15 mg/kg/day dose groups, but with incomplete data around effect with 0.03 mg/kg/day. No difference was observed between the 0.10 mg/kg/day and 0.15 mg/kg/day groups, however, a definitive dose-response relationship could not be extrapolated due to the small size of the population sample.

The beneficial effects observed during this study were dependent on GATTEX treatment, as evidenced by the absorption of all measured parameters returning toward baseline levels after the short-term, 21-day intervention was discontinued (GI fluid absorption shown in Figure 15).

Figure 15. Changes in GI Fluid Absorption During and After Withdrawal of GATTEX Treatment (Study 92001)



Findings from intestinal biopsies obtained in phase 3 Study 004 affirmed the pharmacodynamic effect of GATTEX (also discussed in Section 6.3.3.6). In Study 004, GATTEX treatment for 24 weeks in SBS subjects induced expansion of the absorptive epithelium by increasing villus height in the small intestine (GATTEX 0.05 mg/kg/day [p=0.0065] and GATTEX 0.10 mg/kg/day [p=0.0024]). The composition of the GATTEX mucosa did not differ from placebo when expressed on a mucosal mass basis, indicating that these structural adaptations involved the production of additional tissue that did not differ in cellular size or composition from what was originally present. Histopathological evaluation of the intestinal tissue samples demonstrated no development of dysplastic changes.

Effects on Plasma Citrulline

Successful oral adaptation in patients with SBS that allows nutrients to directly interact with the intestine will require an increase in enterocyte mass and/or surface area. Expansion of normal intestinal epithelium can be demonstrated with increases in villous height and crypt depth, as discussed in the previous section. These increases may be reflected in increases in citrulline, an amino acid produced by enterocytes, considered to be a putative biomarker of enterocyte mass (Crenn et al, 2000; Crenn et al, 2003; Crenn et al, 2008). Therefore, citrulline was evaluated as a potential pharmacodynamic parameter after GATTEX treatment (i.e., an increase in citrulline levels reflects an increase in enterocyte mass).

Following GATTEX treatment in healthy subjects (Study 015) and SBS subjects (in Study CL0600-020 [hereafter referred to as Study 020], Study CL0600-021 [hereafter referred to as Study 021], Study 004, and CL0600-005 [hereafter referred to as Study 005] increases from baseline in plasma citrulline levels were observed. In subjects with SBS, plasma citrulline increased to levels found in the normal population (12 to 30 µmol/L) (Study 004) (data shown in Section 6.3.2.6). Similarly, SBS subjects in Study 020 showed an increase of 20.6 µmol/L (from 18.4 µmol/L at baseline) in plasma citrulline after 24 weeks of treatment.

The observed citrulline data indicate increasing enterocyte mass, combined with the morphological evidence for increasing the surface area of the intestinal epithelium by increasing villus height and crypt depth, provide a basis for the increased absorption and decreased fecal losses of fluids and nutrients as demonstrated in Study 92001.

Gastric Emptying

GATTEX 4 mg SC once daily for 10 days had no effect on gastric emptying as measured by acetaminophen absorption kinetics in a randomized, double-blind, placebo-controlled, parallel group study in 36 healthy volunteers (Study C10-003).

Metabolic Effects

Study C10-003 assessed the effects of GATTEX on insulin, glucagon, and glucose. In Study C10-003, no clinically relevant changes were seen in postprandial glucose, insulin, and glucagon blood levels.

Cardiac Repolarization

The potential of a drug to delay cardiac repolarization can be measured as prolongation of the QT/corrected QT (QTc) interval (CHMP/ICH/2/04; EMEA/CHMP/ICH/310133/2008). Study C09-001 investigated any potential effect of GATTEX on the QTc interval and cardiac conduction (RR, PR, and QRS) in healthy subjects. Single SC doses of GATTEX 5 and 20 mg had no effect on cardiac repolarization as determined by electrocardiogram (ECG)-derived measurements of QTcF (QT interval corrected for heart rate using Fridericia's formula). The effect of GATTEX on cardiac repolarization (QTcF interval) was comparable to placebo, while moxifloxacin, the positive control, showed the expected prolongation in QTcF (described in detail in Section 9.7).

5.0 Overview of Clinical Development Program

Table 6 provides details for the phase 3 studies that provide evidence for the efficacy of GATTEX 0.05 mg/kg/day for the treatment of SBS, including:

- two 24-week phase 3 studies – Study 004 and Study 020,
- a completed long-term extension study to Study 004 (Study 005), and
- an ongoing extension study to Study 020 (Study 021).

Findings from the clinical pharmacology Study 92001 formed the basis for the design of Study 004. The first subject of Study 004 (the first phase 3 study) enrolled on 25 May 2004 and the last subject completed the study on 06 July 2007. Study 020 was conducted as a pivotal confirmatory trial of the 0.05 mg/kg/day dose and enrolled the first subject on 25 November 2008 and completed the last subject on 04 January 2011.

A detailed description of the study design, efficacy endpoints, and statistical methods is presented in Section 6.1 for Study 004 and Section 7.1 for Study 020. A brief overview of these studies is provided below.

Studies 004 and 020 were prospective, randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter studies. The population enrolled in these studies was adult subjects with SBS due to intestinal resection who were dependent on parenteral support for at least 12 months (including PN/IV support) and for at least 3 times per week. The studies were conducted in the US, Canada, and Europe at a total of 32 and 27 centers for Studies 004 and 020, respectively. Investigators and study personnel at each of these centers were qualified in the treatment of SBS. The underlying cause and severity of SBS were also comparable among centers and the results from subjects treated in non-US centers are representative of and could be generalized to the population of adults with SBS in the US.

Eligible subjects (i.e., those who maintained a stable PN/IV volume, as indicated by a targeted urine output of 1.0-2.0 L/day, for at least 4 consecutive weeks) were randomized into a 24-week treatment phase. In Study 004, subjects were randomized in a 2:2:1 ratio to GATTEX 0.05 mg/kg/day, GATTEX 0.10 mg/kg/day, or matching placebo, respectively. In Study 020, subjects were randomized in a 1:1 ratio to GATTEX 0.05 mg/kg/day or placebo.

Table 6. Listing of Individual Phase 3 Clinical Studies

Study No. Number of Centers Locations	Study Start and Stop Dates No. Subjects Randomized/ Planned	Study Design Type of Control	Study Objective	Test Product(s); Control Dose, Route and Regimen	No. Subjects by Arm Entered / Completed	Total Duration of Treatment	Diagnosis Inclusion Criteria	Primary Endpoint(s)
Study 004 32 centers US, Canada, & Europe	Study initiation date: 25 May 2004 Study completion date: 06 July 2007 84[a]/ 80	MC, R, DB, parallel group, PC study	To evaluate the efficacy, safety, tolerability and pharmacokinetics of GATTEX compared with placebo in subjects with PN/IV-dependent SBS.	A: GATTEX 0.05 mg/kg/ day SC B: GATTEX 0.10 mg/kg/ day SC C: Dose-matching placebo Study drug was to be administered once daily into 1 of the 4 quadrants of the abdomen or either thigh	A: 35/27 B: 33/29[a] C: 16/15	24 weeks	Male or female subjects, aged 18 years or older, with SBS and PN/IV fluid required at least 3 times week	The primary efficacy variable was an ordered categorical (or graded) response that accounted for both intensity (>20% to 100% reduction in PN/I.V. volume from baseline) and duration (response at Weeks 16 and 20 and Weeks 20 and 24) of the response at the end of the 24-week treatment period.
Study 020 27 centers US, Canada, & Europe	Study initiation date: 25 Nov. 2008 Study completion date: 04 Jan. 2011 86[b]/ 86	MC, R, DB, parallel group, PC study	To evaluate the efficacy, safety, tolerability, and pharmacodynamics of GATTEX compared with placebo in subjects with PN/IV-dependent SBS	A: GATTEX 0.05 g/kg/ day SC B: Dose-matching placebo Study drug was to be administered once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm	A: 43[b]/39 B: 43/39	24 weeks	Male or female subjects, aged 18 years or older, with SBS and PN/IV fluid required at least 3 times week	The primary efficacy variable was the percentage of subjects who were considered responders (i.e., a reduction of 20% to 100% in PN/IV volume from baseline) at Weeks 20 and 24.

Table 6. Listing of Individual Phase 3 Clinical Studies (Continued)

Study No. Number of Centers Locations	Study Start and Stop Dates No. Patients Randomized/ Planned	Study Design Type of Control	Study Objective	Test Product(s); Control Dose, Route and Regimen	No. Patients by Arm Entered / Completed	Total Duration of Treatment	Diagnosis Inclusion Criteria	Primary Endpoint(s)
Study 005 23 centers US, Canada, & Europe	Study initiation date: 10 Jan. 2005 Study completion date: 24 Jan. 2008 65[c]	MC, R, DB extension study of CL0600-004	To evaluate the long-term safety and efficacy of once daily administration of GATTEX in subjects with PN/IV-dependent SBS	A: GATTEX 0.05 mg/kg/ day SC[d] B: GATTEX 0.10 mg/kg/day SC[d] C: GATTEX 0.05 mg/kg/day SC D: GATTEX 0.10 mg/kg/day SC Study drug was to be administered once daily, into 1 of the 4 quadrants of the abdomen or either thigh	A: 6/6 B: 7/5 C: 25/20 D: 27/23	28 weeks	Subjects with PN/IV-dependent SBS who completed Study 004	The primary objective of this study was to evaluate the long-term safety and tolerability of daily GATTEX dosing for up to 12 months in adult subjects with SBS who were dependent on PN/IV fluid. Key secondary efficacy variables focused on reductions in PN/IV volume.
Study 021 25 centers US, Canada, & Europe	Study initiation date: 21 Sept. 2009 Study completion date: Ongoing 88 as of the data cutoff of 30 June 2011	MC, OL, extension study of CL0600-020	To evaluate the long-term safety and efficacy of once daily administration of GATTEX in subjects with PN/IV- dependent SBS	GATTEX 0.05 mg/kg/day SC administered once daily, into 1 of the 4 quadrants of the abdomen or either thigh	88 (37 on GATTEX 0.05 mg/kg and 51 on placebo or not treated in Study 020)	2 years	Subjects with PN/IV-dependent SBS participating in Study 020 who completed the study, DCd dosing prematurely due to non-drug related AE, or were in Stage 1 of the study after target number of subjects had been randomized	The primary objective of this study was to evaluate the long-term safety and efficacy of daily GATTEX dosing for up to 24 months in adult subjects with SBS who were dependent on PN/IV fluid.

Table 6. Listing of Individual Phase 3 Clinical Studies (Continued)

AE = adverse event, DB = double-blind; MC = multicenter; No. = number; OL = open-label; PC = placebo-controlled; PN/IV = parenteral nutrition/intravenous fluids; R = randomized; SBS = short bowel syndrome; SC = subcutaneous

a. A total of 83 subjects were randomized and received study drug. One subject from Study 004 who was randomized to GATTEX 0.10 mg/kg/day did not receive study drug.
b. A total of 85 subjects were randomized and received study drug. One subject from Study 020 who was randomized to GATTEX 0.05 mg/kg/day did not receive study drug.
c. The maximum sample size for this study was the number of subjects who were randomized and completed the 24 weeks of Study 004. All consenting subjects who completed Week 24 of Study 004 were eligible to enroll in this study; 65 subjects were enrolled in this study and all were analyzed for efficacy and safety.
d. Subjects who received placebo during Study 004 were randomized to GATTEX in Study 005.

5.1 Differences in Study Design Between Study 004 and Study 020

5.1.1 Randomization

Randomization was stratified in both studies by PN/IV fluid consumption at Baseline, however, the stratification variable differed between the two phase 3 studies. In Study 004, randomization was stratified by 3 PN/IV consumption levels at Baseline (i.e., IV fluids 3 to 7 times weekly; PN/IV 3 to 5 times weekly; and, PN/IV 6 to 7 times weekly). Thus, subjects were randomized across centers rather than within a center. Placebo subjects also received a randomization assignment for either GATTEX 0.05 mg/kg/day or 0.10 mg/kg/day in the event that they entered Study 005. In Study 020, randomization was stratified by 2 PN/IV consumption levels at Baseline (i.e., ≤6 L/week, >6 L/week).

5.1.2 Weaning Algorithms

In both placebo-controlled studies (020 and 004), investigators were to modify PN/IV volume based on protocol specified guidance using 48-hour urine output measured prior to each dosing visit. Although the guidance regarding the PN/IV volume reduction algorithms were generally similar between the studies, 2 key modifications were made to the algorithm in Study 020, based on observations in Study 004, which suggested that an earlier and greater adjustment of PN/IV volume would provide more optimal weaning of PN/IV therapy. The reasons for a broader range of adjustment in the PN/IV volume reduction algorithm was to ensure that when necessary an adjustment could be made to properly address clinical situations that needed attention (i.e., an early increased urine output).

In Study 004, reductions in PN/IV volume were to be no more than 10% of the stabilized baseline PN/IV volume (unless urine output was more than 2.0 L/day and at least 10% greater than at baseline, at which point investigators could reduce PN/IV volume by more than 10% to a clinically appropriate amount) (details provided in Section 6.1).

Because of experience in Study 004 where increased absorption appears to have led to decreased oral intake early in the study, changes in the weaning algorithm were made to Study 020. In Study 020, reductions in PN/IV volume could begin at week 2 and be up to 30% of the stabilized baseline PN/IV volume (details in Section 7.1).

5.1.3 Primary Efficacy Endpoint

The efficacy endpoints for Studies 004 and 020 were related to a 20% or greater reduction from baseline PN/IV volume at various subsequent study time points.

For Study 004, the original protocol stated that the primary efficacy endpoint was to be a responder analysis, as was the case in the subsequent Study 020. However, the primary efficacy endpoint was modified (based on protocol amendments that were finalized prior to the blind being broken) to incorporate both the intensity and duration of the reduction in PN/IV volume (i.e., graded response) (see Section 6.1.3.1 for details). The responder analysis was retained as a secondary efficacy analysis in Study 004.

For Study 020, the primary efficacy endpoint was the percentage of subjects who demonstrated a clinically relevant response (i.e., a reduction of 20% to 100% from baseline in PN/IV volume) at Week 20 AND Week 24 of treatment. Subjects who met this criterion were deemed "responders". Two panels of clinical experts including recognized leaders in the fields of Gastroenterology and Clinical Nutrition and who actively care for SBS patients, were convened by NPS and affirmed the clinical meaningfulness of the criterion of 20% reduction in PN/IV volume.

5.2 Dose Selection for Phase 3 Studies

The choice of dose for Study 004 was based upon the results of Study 92001 wherein a highly significant increase in GI fluid absorption of approximately 750 to 1000 mL/day (corresponding to a relative increase of up to 30%) was observed at the end of treatment with doses of 0.10 and 0.15 mg/kg/day (described in Section 4.3). The 0.10 mg/kg/day dose was selected as the dose that showed the most consistent effect in SBS subjects in Study 92001. For Study 004, a lower dose of 0.05 mg/kg/day was included.

In Study 020, the dose of 0.05 mg/kg/day was chosen to confirm the results from Study 004 observed in the corresponding dose group. In Study 004, the 0.10 mg/kg/day dose provided no additional clinical benefit compared to that with the 0.05 mg/kg/day dose (Section 6.3.1); both GATTEX doses reduced PN/IV volume reduction by 2.5 L versus 0.9 L for placebo. Therefore, 0.05 mg/kg/day of GATTEX was selected as the dose for Study 020.

In both studies, GATTEX or placebo was administered by SC injection once daily into 1 of the 4 quadrants of the abdomen, either thigh, and in Study 020 only, also into either arm.

5.3 Long-term Extension Studies

A detailed description of the study design, efficacy endpoints, and statistical methods is presented in Appendix B for Studies 005 and 021. A brief overview of these studies is provided below.

In addition to the placebo-controlled phase 3 studies, extension Study 005 provides further evidence of the sustained efficacy of GATTEX 0.05 mg/kg/day. Specifically, subjects who completed 24 weeks of treatment in Study 004 were eligible to enter this 28-week, randomized, double-blind, parallel-group, multinational, multicenter extension study. Subjects who received GATTEX in Study 004 continued to receive the same blinded dose of GATTEX during Study 005. Subjects who received placebo in Study 004 were randomized in a 1:1 ratio to GATTEX 0.05 mg/kg/day or 0.10 mg/kg/day in Study 005. The randomization for the GATTEX dose of Study 005 for subjects receiving placebo in Study 004 occurred at the time of randomization for Study 004. Although no primary efficacy variable was prospectively defined for Study 005, various efficacy endpoints (including response rate) were measured to assess the maintenance and durability of the effect of GATTEX.

Study 021 is an ongoing long-term extension of Study 020 (interim report database cut-off of 30 June 2011 for NDA). Study 021 is an open-label, multinational, multicenter

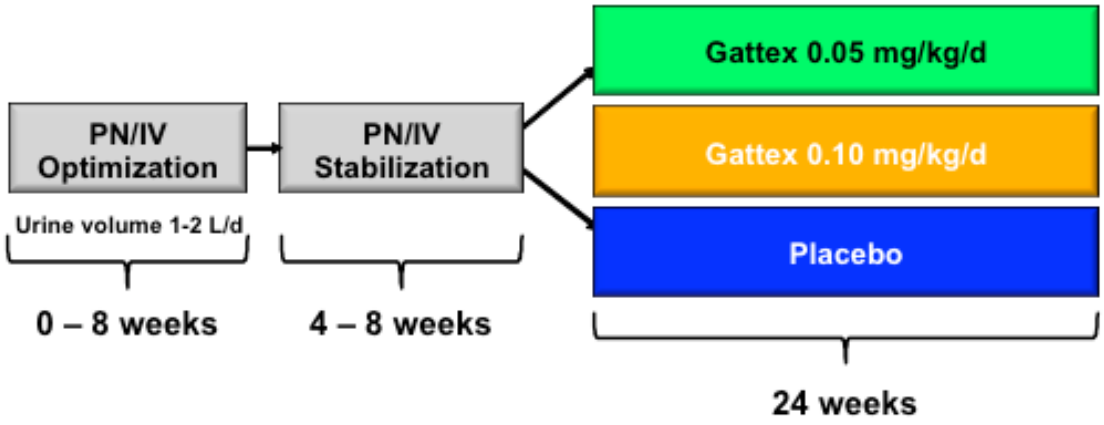
study that enrolled subjects who completed 24 weeks of dosing in Study 020, or successfully completed stage 1 (optimization/stabilization) in Study 020 (i.e., qualified for randomization) after the target number of approximately 86 subjects had been randomized. All subjects received GATTEX 0.05 mg/kg/day SC administered once daily, into 1 of the 4 quadrants of the abdomen or either thigh or arm. Similar to Study 005, no primary efficacy variable was prospectively defined for Study 021, however various efficacy endpoints around further PN/IV volume reductions (including response rate and complete weaning off) are being measured to provide further evidence of the maintenance and durability of the effect of GATTEX for SBS over the long term.

6.0 Efficacy Findings in Study 004

6.1 Study Design

Study 004 was a randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter study (Figure 16). The study consisted of a screening visit, a PN/IV fluid volume-optimization period, a stabilization period (which was designed to demonstrate a stable administration of PN/IV for 4 weeks that could be utilized to establish Baseline), a subsequent 24-week treatment period, and a 4-week follow-up period (for subjects not electing to participate in the extension Study 005). Subjects completing this study had the option to enroll into extension Study 005 for an additional 28 weeks of treatment.

Figure 16. Study Design – Study 004



PN/IV= Parenteral nutrition/intravenous fluids
Source: CSR Study 004

Urine output and oral fluid intake were measured during the Screening visit over a 48-hour period. If at Screening subjects did not have a stable PN/IV volume as indicated by a targeted urine output of 1.0-2.0 L/day, they entered an optimization period (8 weeks maximum). The purpose of the optimization period was to establish each subject's optimized baseline PN/IV fluid volume that would result in urine output between 1.0 and

2.0 L/day. Following the optimization period, all subjects entered a 4- to 8-week stabilization period during which they were maintained on the stabilized, tolerated PN/IV volume. Subjects who demonstrated PN/IV volume stability for at least 4 consecutive weeks (see Inclusion Criterion 7 below for stability criteria) were eligible for randomization and entry into the treatment period. If a subject failed to remain stable for at least 4 consecutive weeks immediately prior to randomization, the subject was allowed to start the optimization period again. Those subjects who failed to stabilize after 2 attempts were not randomized.

If subjects were able to be optimized and could maintain their urine output (1-2 L/day) for the stabilization period on this regimen, they were then allowed to be randomized in a 1:2:2 ratio to placebo, GATTEX 0.05 mg/kg/day, or GATTEX 0.10 mg/kg/day. Randomization was stratified by PN/IV consumption level at baseline (Level 1: IV fluids 3 to 7 times weekly; Level 2: PN/IV 3 to 5 times weekly; Level 3: PN/IV 6 to 7 times weekly). Thus, subjects were randomized across centers rather than within a center. During the 24-week treatment phase, each subject's PN/IV volume was evaluated for possible adjustment, which was adjusted once every 4 weeks (Weeks 4, 8, 12, 16, and 20) based on protocol-directed guidance, with PN/IV volume increased if urine output was less than 1.0 L/day or less than Baseline level and decreased by 10% of the optimized baseline PN/IV volume if urine output increased by at least 10% from Baseline. Since Study 004 was the first phase 3 study to assess the ability of GATTEX to reduce PN/IV volume, this limit (i.e., no more than a 10% reduction in PN/IV volume) was set to guard against dehydration. PN/IV volume adjustments outside the guidance were allowed if deemed medically necessary by the investigator. The protocol also stipulated that oral fluid intake during the 48-hour urine output measurement period should be consistent with oral fluid intake at Baseline.

6.1.1 Evaluation of PN/IV Parameters

All subjects measured PN/IV volumes on a daily basis between the clinical visits, recording the values in diaries. Each diary was transcribed onto the CRF at each visit. The weekly PN/IV volume was calculated in 2-week intervals since the PN/IV prescribed

volume prescription from the physician could stipulate dosing over 2 weeks (because of some days on and some days off PN/IV).

The "weekly" PN/IV volume calculation was:

> Weekly PN/IV volume for 14 days = [sum (PN/IV volume for 14 days)/14 days)] x 7 days. If < 14 days of data recorded = [(sum of PN/IV volume for x days prior to following visit)/(number of days summed)] x 7.

Subjects also measured 48-hour fluid intake and 48-hour urine output at home immediately prior to scheduled visits and recorded these values in their diaries.

To ensure safety of PN/IV reduction, all subjects were checked for clinical stability following each reduction in PN/IV: These measures included 48-hour oral fluid intake, 48-hour urine output, urine sodium, hematocrit, blood urea nitrogen (BUN), creatinine, and serum prealbumin. If there was evidence of dehydration, the PN/IV was to be restored to the previous level. While fluid reduction could have been adjusted based upon urine output, hematocrit, and markers of renal function, measurements to ensure safety in the adjustments of nutritional requirements were commonly made based on body weight and absence of clinical signs and symptoms of dehydration.

6.1.2 Subject Population – Inclusion and Exclusion Criteria

Approximately 125 subjects were to be screened to provide 80 randomized subjects. The inclusion and exclusion criteria for Study 004, as detailed below, were similar to those for Study 020 (in Section 7.1.1).

Inclusion Criteria

This study was to enroll subjects who meet the following criteria:

1. Signed and dated informed consent form (ICF) before any study-related procedures are performed
2. Men and women aged 18 years or older at the time of signing the ICF

3. SBS as a consequence of major intestinal resection (e.g., due to injury, volvulus, vascular disease, cancer, Crohn's disease)
    a. For subjects with a history of cancer (exceptions listed in Exclusion Criteria), the subject was to be disease-free for at least 5 years
    b. For subjects with a history of Crohn's disease, the subject was to be in clinical remission, as determined by clinical assessment
4. Body weight was to be less than 88 kg at the time of enrollment
5. Subjects who had undergone major intestinal resection resulting in PN/IV fluid dependency for at least 12 continuous months prior to dated signature of ICF (Minor ostomy revisions within this time period were allowable)
6. PN/IV fluid required at least 3 times weekly to meet their caloric, fluid, or electrolyte needs due to ongoing malabsorption
7. Stable for at least 4 consecutive weeks immediately prior to randomization based upon the following:
    a. Usage and volume of PN/IV
    b. 48-hour urine output (1.0 to 2.0 L/day)
    c. Urine sodium (greater than 20 mmol/day)
    d. Adequate renal function (serum creatinine and BUN are 1.5 x upper limit of normal [ULN] or less)
    e. Hematocrit indicating satisfactory hydration (ULN or less)
    f. Motility altering medications
    g. BMI was 18 to 27 kg/m^2
    h. Adequate hepatic function (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] were less than 2.0 x ULN; total bilirubin was less than 1.25 x ULN; and alkaline phosphatase was less than 2.5 x ULN)
8. Female subjects who were not surgically sterile or postmenopausal must use medically acceptable methods of birth control during and for 30 days after the treatment period. Postmenopausal was defined as aged 60 years or older and at least 2 years must have elapsed since the last menses.

Exclusion Criteria

Subjects who met any of the following criteria were excluded:

1. History of cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state. This did not include resected cutaneous basal or squamous cell carcinoma, or in situ cervical cancer
2. History of alcohol or drug abuse (within previous year)
3. Participation in a clinical study within 30 days prior to signing the ICF, or concurrent participation in any clinical study

4. Clinically significant laboratory abnormalities at the time of randomization
5. Previous use of GATTEX
6. Prior use of GLP-2 within 3 months of screening visit
7. Hospital admission within 1 month prior to screening visit.
8. Pregnant or lactating women.
9. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results.
10. Presence of any of the excluded disease states described in the table below.
11. Failure to adhere to required washout periods for medications: 12-week washout for monoclonal antibody therapy (e.g., infliximab) and growth hormone or growth factors; 30-day washout for systemic corticosteroids (short tapering courses possible), other biologics, methotrexate, cyclosporine, tacrolimus (FK506), sirolimus, octreotide, IV glutamine, and any other investigational drugs.

Excluded Diseases and Illnesses

Body system	Conditions excluded
Related to SBS	Radiation enteritis; scleroderma; celiac disease; refractory or tropical sprue; pseudo-obstruction
Gastrointestinal (GI)	Active inflammatory bowel diseases (IBD); pre-malignant or malignant change in colonoscopy biopsy or polypectomy; surgery scheduled within the time frame of the study
Immune	Human immunodeficiency virus (HIV)-positive test; immunological disorders
Cardiovascular, respiratory, renal, endocrine, hepatic, or central nervous system	Significant active, uncontrolled, untreated systemic diseases

6.1.3 Definitions of Efficacy Endpoints

6.1.3.1 Primary Endpoint

The primary efficacy variable was a graded response score (a scoring algorithm that takes both response intensity and duration between Weeks 16 and 24 into account).

The intensity of response relied on a reduction from Baseline in weekly PN volume, where the protocol-defined reduction was set at a minimum of 20% and a maximum of 100%. Duration of response incorporated the responses at Weeks 16 to 20 and Weeks 20 to 24.

Values for the response criterion are depicted below:

	Weeks 20 and 24			
Weeks 16 and 20	**<20% Reduction**	**20%-39% Reduction**	**40%-99% Reduction**	**100% Reduction**
<20% Reduction	0	1	2	3
20%-39% Reduction	0	2	3	4
≥40% Reduction	0	3	4	5

6.1.3.2 Secondary Endpoints

The secondary variables were:

- number and percentage of subjects who demonstrated a response at Week 20, and who maintained that response at Week 24. Response was defined as the achievement of at least a 20% reduction from Baseline in weekly PN volume (original primary efficacy endpoint in Study 004 and primary efficacy endpoint of Study 020);
- number and percentage of subjects who achieved at least a 1-day reduction in weekly PN;
- absolute reduction from Baseline in weekly PN kilojoules (transformed from kilocalories);
- absolute reduction from Baseline in weekly volume of PN;
- change from Baseline in plasma citrulline at Week 24;

- intestinal absorption of fluid, energy, nitrogen, fat, carbohydrate, sodium, potassium, magnesium, and calcium at Weeks 8 and 24 (at a subset of selected study centers)

6.1.3.3 Exploratory Endpoints

Exploratory efficacy endpoints included: time to a 20% reduction in PN volume; time to discontinuation of PN; time to a 1-day reduction in weekly PN; number and percentage of subjects with reduced IV catheter access at Week 24; change from Baseline in QoL at Weeks 4, 8, 12, 16, 20, and 24; and, mucosal crypt-villus architecture and cellular composition within the small and large intestine. Quality of life (QOL) was assessed by the following: 36-item Medical Outcome Survey (SF-36) (Ware and Sherbourne, 1992), the Inflammatory Bowel Disease Questionnaire (IBDQ) (De Boer et al, 1995), and the abbreviated EuroQol (1990).

6.1.4 Statistical Methods

6.1.4.1 Sample Size and Powering

A sample size of 80 randomized subjects (32 subjects in each of the GATTEX treatment groups and 16 subjects in the placebo group) was to provide at least 90% power to detect an increase in the percentage of subjects who had the protocol-defined minimum response (20% decrease for both Weeks 20 and 24), from 5% in the placebo group to 50% in the GATTEX groups (80% power to detect an increase to 44%). The power calculations were based on 2-sided tests of significance using Fisher's Exact test.

6.1.4.2 Analysis Populations

The intent-to-treat (ITT) population included all randomized subjects who received at least 1 dose of study drug. All efficacy analyses were conducted on this study population. Subjects were included in the treatment group to which they were randomized, regardless of the actual drug they received.

The Safety population included all subjects who received at least 1 dose of double-blind study drug. Subjects were included in the treatment group reflective of the treatment they actually received.

6.1.4.3 Analysis of Primary Endpoint

For the primary efficacy variable, the ordered categorical response variable was summarized for each treatment group using descriptive statistics. Pairwise treatment comparisons were made using a rank analysis of covariance (ANCOVA) (an extension of the Wilcoxon rank sum test) with strata for the Baseline PN/IV consumption level used for the stratification of the randomization and treatment group with the Baseline weekly PN volume as a covariate, and a step-down procedure for multiple comparisons (Fleiss et al, 2003; Koch et al, 1998; Stokes et al, 1995). A step-down procedure was to be used to adjust for multiple comparisons when testing multiple hypotheses of treatment effect. In this procedure, the high-dose vs. placebo comparison needed to be significant at a p=0.05 level before testing the low-dose vs. placebo.

6.1.4.4 Analysis of Secondary and Exploratory Endpoints

The secondary variable, response at both Week 20 and Week 24, defined as at least a 20% reduction from Baseline in weekly PN volume, was summarized by the number and percentage of responders and the corresponding 95% confidence interval (CI) of the percentage for each treatment group. Pairwise differences between the rates and the corresponding 95% CIs were presented. Pairwise comparisons between treatment groups were made using Fisher's Exact Test. For rates, treatment group comparisons were made using a rank ANCOVA (an extension of the Wilcoxon rank sum test) with strata for Baseline PN consumption level used for the stratification of the randomization and with the Baseline weekly PN volume as a covariate and the step-down procedure. Center was not included in the model because the number of subjects within a center was small.

Descriptive statistics (e.g., n, mean, standard deviation, median, minimum, and maximum values for continuous variables and numbers and percent of subjects in specified

categories for discrete variables) and the corresponding 95% CIs were used to summarize the absolute values, change from Baseline, and rates at designated time points for each treatment group. For change from Baseline variables, pairwise differences between treatment groups and the corresponding 95% CIs utilized estimates from a 2-way repeated measures ANCOVA. The model included effects for Baseline PN/IV stratification of the randomization, treatment group, visits and Baseline weekly PN/IV volume as covariates.

Time to an event (e.g., a 20% reduction in weekly PN volume, a 1-day reduction in PN volume) was evaluated using a life-table analysis. The treatment group comparisons were made using the log rank and Wilcoxon tests.

6.1.4.5 Subgroup Analyses of Efficacy

The expanded efficacy variable was summarized by descriptive statistics for the following subgroups: age, race, and gender.

6.1.4.6 Handling of Dropouts or Missing Data and Robustness

For the analysis of the primary efficacy variable (ordered categorical response variable), subjects who drop out of the study prior to the end of the 24 week dosing period were included with an assumption of zero for the response variable, i.e., the least desirable of the 6 levels.

For safety variable, a last visit time point, with each subject's last observation included as their observation, were analyzed in addition to the scheduled visits.

The method proposed for sensitivity analysis of the quantitative weekly PN volume, was to run the primary efficacy analyses by replacing the missing weekly PN volumes with PN volumes that are recorded within the specified month for the subjects with less than 9 available data points. The data were obtained by going back in time, before the last 2 weeks of the specified month, until 9 data points were obtained. If there are still not enough data points, then the subject was considered a 'failure' for that month. This

method preserves the spirit of the data collection from the diary, using as much data that the subject actually recorded in the diary.

Diary data for the recording of the PN volume may not be reliable, depending on the cooperation of the subjects and the sites enrolled in the study. If the diary data were found to be unreliable (more than 50% of the data is not usable), then the weekly prescribed PN volume for all subjects were used to examine the impact of using the physician prescription vs. the daily diary recordings of the subjects. There is an important caveat to this analysis in that subjects who have a large amount of missing data will benefit "more" with this "preset" data which may introduce a bias for those subjects with more missing data.

Robustness of analyses of the expanded primary efficacy outcome: These analyses concern potential sources of bias other than missing values that might be induced by violations of protocol adherence. For example, subjects assigned to GATTEX who are not compliant with their treatment, or subjects assigned to placebo who are similarly non-compliant can cause results of the ITT analysis to deviate substantially from results of the PP analysis. A likely impact of such deviations would be that typical responses in each study group move towards one another, yielding an overall smaller effect. Methods to identify the impact of such non-compliance include performing study analyses on data sets obtained by excluding subjects identified as not adhering to the protocol. Essentially a PP analysis was performed on the data, including the descriptive statistics. However, it may not be informative to run the rank ANCOVA on this data if there are few subjects in this sample. With sample sizes of approximately 32 in each GATTEX group and 16 in the placebo group for the ITT population, the natural decrease in these numbers for the PP population may not lend itself to an effective analysis and the power of the test would surely decrease.

6.1.4.7 Multiple Comparisons/Multiplicity

The two GATTEX treatment groups (0.10 mg/kg/day, 0.05 mg/kg/day) were each compared to the placebo group.

The following step-down procedure was used to adjust for multiple comparisons in the primary efficacy analysis:

Step 1: The 0.01 mg/kg/day GATTEX group was compared with the placebo group using a two-sided test, and a 0.05 significance level.

- If the 0.10 mg/kg/day GATTEX group was not statistically significantly different from the placebo group, no further comparisons were made.
- If the 0.10 mg/kg/day GATTEX group was statistically significantly different from the placebo group, comparisons continued in step 2.

Step 2: The 0.05 mg/kg/day GATTEX group were compared with the placebo group using a two-sided test, and a 0.05 significance level.

- If the 0.05 mg/kg/day GATTEX group was not statistically significantly different from the placebo group, no further comparisons were made.
- If the 0.05 mg/kg/day GATTEX group was statistically significantly different from the placebo group, comparisons continued in step 3.

Step 3: The 0.10 mg/kg/day GATTEX group was compared with the 0.05 mg/kg/day GATTEX group using a two-sided test, and a 0.05 significance level.

6.2 Subject Disposition, Demographics, Other Baseline Characteristics, and Concomitant Medications Taken During the Study

6.2.1 Subject Disposition

A total of 139 subjects were screened at 32 study centers (1 in Belgium, 4 in Canada, 1 in Denmark, 3 in Germany, 3 in France, 1 in England, 1 in Netherlands, 3 in Poland, 15 in US) for this study. Of these 139 subjects, 84 subjects were randomized and 55 subjects were screen failures.

The first subject was screened on 25 May 2004, and the last subject's evaluations were performed on 06 July 2007.

Of the 84 randomized subjects, 71 subjects completed 24 weeks of the study. One subject who was randomized (to the GATTEX 0.10 mg/kg/day group) did not receive study drug. Thus, a total of 83 subjects were randomized into the study and received study drug (ITT and Safety analysis populations).

The specific reasons for discontinuation are summarized in Table 7. One, 5, and 2 subjects in the placebo, GATTEX 0.05 mg/kg/day, GATTEX 0.10 mg/kg/day groups, respectively, discontinued prematurely due to a treatment-emergent adverse event (AE).

Table 7. Subject Disposition in Study 004 - All Subjects Screened

Category	Placebo	GATTEX 0.05 mg/kg/day	GATTEX 0.10 mg/kg/day	All Subjects
Randomized, n	16	35	33	84
Treated, n	16	35	32	83
Completed dosing period, n (%)	15 (93.8)	27 (77.1)	29 (90.6)	71 (85.5)
Discontinued prematurely, n (%)	1 (6.3)	8 (22.9)	3 (9.4)	12 (14.5)
Adverse event	1 (6.3)	5 (14.3)	2 (6.3)	8 (9.6)
Subject decision	0	3 (8.6)	1 (3.1)	4 (4.8)
Lost to follow-up	0	0	0	0
Investigator decision	0	0	0	0
Death	0	0	0	0
Other	0	0	0	0

Source: CSR Study 004, Table 14.1.1.7

The ITT analysis population included the 83 subjects who were randomized and treated: 16 in the placebo group; 35 in the GATTEX 0.05 mg/kg/day group; and, 32 in the GATTEX 0.10 mg/kg/day group.

6.2.2 Demographic Characteristics

In general, baseline demographic data were similar to the US population among the treatment groups (Table 8). The majority of subjects in the ITT population were Caucasian (77/83 subjects, 92.8%). Mean (SD) age was 48.8 (14.2) years, with 38.6% (32/83 subjects) ≥ 55 years of age. The population was 55.4% female (46/83 subjects). There were no statistically significant differences across treatment groups in any of the demographic characteristics at baseline.

Table 8. Demographics Characteristics – Study 004 (Intent-to-Treat Population)

Parameter	Placebo (N=16)	GATTEX 0.05 mg/kg/day (N=35)	GATTEX 0.10 mg/kg/day (N=32)	All Subjects (N=83)
Age (years)				
Mean (SD)	49.4 (15.1)	47.1 (14.2)	50.3 (14.0)	48.8 (14.2)
Min, Max	20, 72	20, 68	19, 79	19, 79
Gender, n (%)				
Male	7 (43.8)	17 (48.6)	13 (40.6)	37 (44.6)
Female	9 (56.3)	18 (51.4)	19 (59.4)	46 (55.4)
Race, n (%)				
Caucasian	15 (93.8)	32 (91.4)	30 (93.8)	77 (92.8)
Black	1 (6.3)	3 (8.6)	2 (6.3)	6 (7.2)
PN/IV consumption level[a], n (%)				
IV fluids 3-7 x weekly	4 (25.0)	8 (22.9)	3 (9.4)	15 (18.1)
PN/IV 3-5 x weekly	8 (50.0)	19 (54.3)	18 (56.3)	45 (54.2)
PN/IV 6-7 x weekly	4 (25.0)	8 (22.9)	11 (34.4)	23 (27.7)
Body weight (kg)				
Mean (SD)	61.5 (8.6)	59.2 (8.7)	59.6 (10.0)	59.8 (9.1)
Min, Max	42, 79	42, 78	44, 80	42, 80
BMI (kg/m^2)				
Mean (SD)	22.0 (2.9)	21.2 (3.0)	21.7 (2.6)	21.5 (2.8)
Min, Max	17, 28	16, 27	17, 26	16, 28

a. At study entry, before optimization and stabilization.

BMI=body mass index, PV/IV=intravenous parenteral nutrition.

Note: p-values for overall treatment comparisons were based on the Fisher's exact test for categorical variables and on a 1-way ANOVA with effect for treatment for continuous variables. The results for p-values were ≥ 0.518 for all treatment comparisons.

Source: CSR Study 004, Table 14.1.2.1

6.2.3 Other Baseline Characteristics

The SBS history for the ITT population is summarized in Table 9. The primary cause for intestinal resection was Crohn's (36.1%, 30/83 subjects) or vascular disease (30.1%, 25/83 subjects). Stoma was present in about a third of subjects (34.9%, 29/83). The mean length ± SD of the remaining small intestine was 65.8 ± 45.4 cm (range: 6 to 200 cm). The colon was included in resection in 27 (32.5%) subjects. Of the 56 (67.5%) subjects with some degree of colon in continuity, 20 (35.7%) had 75% to 100% of the remaining colon and 19 (33.9%) had only >25% to 50% of the remaining colon. The remaining 17 (30.4%) subjects had a degree of colon present between >50% and 75%. Of the 17 (of 56, 20.5%) subjects with distal/terminal ileum, the ileocecal valve was present in 9 (52.9%) subjects and absent in 8 (47.1%) subjects.

Table 9. Short Bowel Syndrome History – Study 004 (Intent-to-Treat Population)

Parameter	Placebo (N=16[a])	GATTEX 0.05 mg/kg/day (N=35[a])	GATTEX 0.10 mg/kg/day (N=32[a])	All Subjects (N=83[a])
Cause of major intestinal resection, n (%)				
Crohn's disease	7 (43.8)	10 (28.6)	13 (40.6)	30 (36.1)
Vascular disease	3 (18.8)	14 (40.0)	8 (25.0)	25 (30.1)
Injury	1 (6.3)	3 (8.6)	2 (6.3)	6 (7.2)
Volvulus	2 (12.5)	5 (14.3)	4 (12.5)	11 (13.3)
Other	3 (18.8)	3 (8.6)	5 (15.6)	11 (13.3)
Stoma, n (%)				
Yes	5 (31.3)	10 (28.6)	14 (43.8)	29 (34.9)
No	11 (68.8)	25 (71.4)	18 (56.3)	54 (65.1)
Type of stoma if present, n (%)				
Jejunostomy	4 (80.0)	6 (60.0)	4 (28.6)	14 (48.3)
Ileostomy	1 (20.0)	2 (20.0)	7 (50.0)	10 (34.5)
Colostomy	0	2 (20.0)	3 (21.4)	5 (17.2)

Table 9. Short Bowel Syndrome History – Study 004 (Intent-to-Treat Population) (Continued)

Parameter	Placebo (N=16[a])	GATTEX 0.05 mg/kg/day (N=35[a])	GATTEX 0.10 mg/kg/day (N=32[a])	All Subjects (N=83[a])
Colon-in-continuity, n (%)				
Yes	11 (68.8)	26 (74.3)	19 (59.4)	56 (67.5)
No	5 (31.3)	9 (25.7)	13 (40.6)	27 (32.5)
Colon amount remaining if present, n (%)				
> 25% - 50%	4 (36.4)	7 (26.9)	8 (42.1)	19 (33.9)
> 50% - 75%	4 (36.4)	9 (34.6)	4 (21.1)	17 (30.4)
> 75% - 100%	3 (27.3)	10 (38.5)	7 (36.8)	20 (35.7)
Remaining small intestine length (cm)				
Mean (SD)	77.3 (52.9)	58.3 (43.6)	68.1 (43.1)	65.8 (45.4)
Min, Max	15, 200	6, 200	10, 200	6, 200
Distal/terminal ileum, n (%)				
Yes	3 (18.8)	6 (17.1)	8 (25.0)	17 (20.5)
No	13 (81.3)	28 (80.0)	23 (71.9)	64 (77.1)
Ileocecal value if distal/terminal ileum present, n (%)				
Yes	1 (33.3)	5 (83.3)	3 (37.5)	9 (52.9)
No	2 (66.7)	1 (16.7)	5 (62.5)	8 (47.1)
Methodology for determining length of remaining anatomy, n (%)				
Surgery	11 (68.8)	20 (57.1)	22 (68.8)	53 (63.9)
Radiology	3 (18.8)	8 (22.9)	3 (9.4)	14 (16.9)
Surgery & radiology	1 (6.3)	4 (11.4)	3 (9.4)	8 (9.6)
Other	0	0	2 (6.3)	2 (2.4)
Not applicable	1 (6.3)	3 (8.6)	2 (6.3)	6 (7.2)

a. For remaining small intestine length, n's are 15, 31, 27, and 73 for placebo, GATTEX 0.05 mg/kg/day, GATTEX 0.10 mg/kg/day, and all subjects, respectively.

Note: Questions for type of stoma and presence of ileocecal valve were only relevant when a distal/terminal ileum was present. Percent of colon remaining was only relevant when the subject had a colon.

Source: CSR Study 004, Tables 14.1.2.11 and 14.1.2.13, Listings 16.2.4.10 and 16.2.4.11

The mean (± SD) **prescribed** weekly PN/IV volume was 11.7 L (± 5.96) at Baseline, and most subjects (71, 85.5%) had central line venous access. About one-fourth of the subjects (23/83, 27.7%) were treated for IV line infections, thrombosis, or occlusions during the 6 months prior to study entry. The mean (± SD) number of hospitalizations for IV line infections was 1.0 (± 1.04). The mean (± SD) number of thrombosis and/or occlusions was 0.5 (± 0.67). Parenteral support at screening is summarized in Table 10.

Table 10. Parenteral Support Status at Screening – Study 004 (Intent-to-Treat Population)

Parameter	Placebo (N=16)	GATTEX 0.05 mg/kg/day (N=35)	GATTEX 0.10 mg/kg/day (N=32)	All Subjects (N=83)
Prescribed weekly PN/IV volume[a] (L)				
Mean (SD)	11.4 (5.72)	10.5 (5.27)	13.1 (6.64)	11.7 (5.96)
Min, Max	5, 25	4, 28	3, 33	3, 33
Estimated weekly PN/IV volume (L)				
Mean (SD)	11.4 (5.74)	10.5 (5.27)	12.9 (6.68)	11.6 (5.96)
Min, Max	5, 25	4, 28	3, 33	3, 33
Type of IV access, n (%)				
Central venous	14 (87.5)	29 (82.9)	28 (87.5)	71 (85.5)
PICC line	1 (6.3)	6 (17.1)	3 (9.4)	10 (12.0)
Other	1 (6.3)	0	1 (3.1)	2 (2.4)
Treated for IV line infections, thrombosis, occlusions in the past 6 months, n (%)				
Yes	3 (18.8)	12 (34.3)	8 (25.0)	23 (27.7)
No	13 (81.3)	23 (65.7)	24 (75.0)	60 (72.3)
Number of IV line infections in the past 6 months				
n	3	12	8	23
Mean (SD)	1.0 (1.00)	1.3 (1.23)	1.1 (0.99)	1.2 (1.09)
Min, Max	0, 2	0, 4	0, 3	0, 4

Table 10. Parenteral Support Status at Screening – Study 004 (Intent-to-Treat Population) (Continued)

Parameter	Placebo (N=16)	GATTEX 0.05 mg/kg/day (N=35)	GATTEX 0.10 mg/kg/day (N=32)	All Subjects (N=83)
Hospitalizations for IV line infections in the past 6 months				
n	3	12	8	23
Mean (SD)	0.3 (0.58)	1.1 (1.16)	1.1 (0.99)	1.0 (1.04)
Min, Max	0, 1	0, 4	0, 3	0, 4
Number of thrombosis and/or occlusions in the past 6 months				
n	3	12	8	23
Mean (SD)	0.3 (0.58)	0.5 (0.67)	0.5 (0.76)	0.5 (0.67)
Min, Max	0, 1	0, 2	0, 2	0, 2
Hospitalizations for thrombosis and/or occlusions in the past 6 months				
n	3	12	8	23
Mean (SD)	0.0 (0.0)	0.2 (0.39)	0.1 (0.35)	0.1 (0.34)
Min, Max	0, 0	0, 1	0, 1	0, 1

a. At study entry before Optimization and Stabilization.

IV=intravenous; PN/IV=parenteral nutrition/intravenous; PICC=Peripheral Intravenous Central Catheter.

Source: CSR Study 004, Tables 14.1.2.15 and 14.1.2.17

The mean **actual** weekly PN/IV volume for the ITT population was 11.1 L (± 6.03) at baseline; subjects in the GATTEX 0.10 mg/kg/day had a higher mean actual weekly PN/IV volume compared with subjects in the GATTEX 0.05 mg/kg/day and placebo groups. (Actual values of PN/IV volume were used for calculating the primary endpoint.)

With regard to medical and surgical history, the most frequently reported GI disorders were small intestinal resection (44.6%), Crohn's disease (36.1%), intestinal anastomosis (32.5%), cholecystectomy (27.7%), SBS (25.3%), partial colectomy (24.1%), and

intestinal resection (24.1%). The most frequently reported non-GI medical/surgical histories were osteoporosis (22.9%), hypertension (19.3%), depression (16.9%), menopause (16.9%), nephrolithiasis (15.7%), and drug hypersensitivity (14.5%). The treatment groups were similar based on medical/surgical history (CSR Study 004, Tables 14.1.2.19 and 14.1.2.20).

6.2.4 Concomitant Medications Taken During the Study

All subjects in the ITT population reported having taken at least 1 concomitant medication during their participation in the study. The most frequently reported concomitant medications (≥15% in either treatment group) were multivitamins, paracetamol, Addamel (an electrolyte and trace element preparation for parenteral nutrition), loperamide, H_2-receptor antagonists (cimetidine, famotidine, ranitidine), heparin, and proton pump inhibitor (omeprazole) (CSR Study 004, Table 14.1.2.23).

6.3 Efficacy Findings in Study 004

6.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study was a graded response score (a scoring algorithm that takes both response intensity and duration at Weeks 16, 20, and 24 into account). The Statistical Analysis Plan (SAP) for Study 004 pre-specified a step-down procedure for the primary efficacy analysis, in which no further statistical testing was to be done if the 0.10 mg/kg/day dose was not significant. The results for the graded response score and associated test statistics are summarized in Table 11 and Table 12, respectively.

The difference between the placebo and GATTEX 0.10 mg/kg/day groups did not meet the level of statistical significance (p=0.161) according to the step-down procedure. However, since a clinically meaningful numerical response (across all graded scores) was observed with the 0.05 mg/kg/day dose and 2 patients were weaned from PV/IV (details given below), the data were further analyzed. The total graded score for the GATTEX

0.05 mg/kg/day group was statistically significantly greater than with placebo (p=0.007, rank-ANCOVA).

Table 11. Summary of Graded Response Score Results – Study CL0600-004 (Intent-to-Treat Population)

Treatment Group	Response Category, n (%)				
	0 No Response	1	2	4	5 Off PN/IV
Placebo	15 (93.8)	0	1 (6.3)	0	0
GATTEX 0.05 mg/kg/day	19 (54.3)	6 (17.1)	6 (17.1)	2 (5.7)	2 (5.7)
GATTEX 0.10 mg/kg/day	24 (75.0)	2 (6.3)	4 (12.5)	2 (6.3)	0

PN/IV = parenteral nutrition/intravenous fluids

Note: One subject was missing the baseline value and could not be ranked.

Source: CSR Study 004, Table 14.2.2.1

Table 12. Test Statistics for the Number and Percentage of Subjects by Graded Response Score – Study 004 (Intent-to-Treat Population)

Comparison[a]	Test Statistic	Degrees of Freedom	p-value	p-value (adjusted)[b]
0.10 mg/kg/day GATTEX vs. Placebo	1.96	1	0.161	0.161
0.05 mg/kg/day GATTEX vs. Placebo	7.32	1	0.007	
0.10 mg/kg/day GATTEX vs. 0.05 mg/kg/day GATTEX	3.06	1	0.080	

a. Test statistic is based on pairwise ANCOVA test after adjustment for the baseline PN/IV consumption level and baseline PN/IV volume as a covariate.

b. p-value is adjusted for multiple comparisons in the primary efficacy analysis.

Note: One subject was missing the baseline value and could not be ranked. Therefore, this subject is not included in the calculation of the test statistic for Rank ANCOVA 0.05 mg/kg/day – Placebo and 0.10 mg/kg/day – 0.05 mg/kg/day GATTEX.

Source: CSR Study 004, Table 14.2.2.1

Two of 16 responders in the 0.05 mg/kg/day group were completely weaned off PN/IV during the 24 weeks of GATTEX treatment (Table 23), 1 having been on PN/IV for approximately 25 years, and the other, for 6.5 years. One subject in the 0.10 mg/kg/day

group, who had been on PN/IV for 3.7 years, discontinued PN/IV at Week 24 (CSR Study 004, Table 14.2.2.1).

6.3.1.1 Subgroup Analyses of Primary Endpoint

Treatment benefit with GATTEX 0.05 mg/kg/day (vs. placebo) was observed across analysis subgroups – age, gender, race, parenteral fluid volume use (IV fluid and electrolytes only 3 to 7 times per week, PN 3 to 5 times per week, PN 6 to 7 times per week, colon in continuity (Y/N), presence of ileocecal valve (Y/N), and percent colon (summarized by quartiles).

6.3.2 Secondary Efficacy Endpoints

6.3.2.1 Efficacy Responders

Key secondary endpoints of Study 004 are summarized in Table 13. The proportion of subjects who were responders (i.e., achieved ≥20% reduction of PN/IV at both Week 20 and Week 24; original primary efficacy endpoint and primary efficacy endpoint of Study 020) was statistically significantly higher in the GATTEX 0.05 mg/kg/day (45.7% [16/35]; p=0.005), but not in the GATTEX 0.10 mg/kg/day (25.0% [8/32]; p=0.172), as compared to placebo (6.3%, 1/16). Protocol constraints that likely affected this finding are discussed in Section 6.3.3.4.

Table 13. Summary of Key Secondary Endpoints – Study 004 (Intent-to-Treat Population)

Secondary Endpoint	Placebo (N=16)	GATTEX 0.05 mg/kg/day (N=35)	GATTEX 0.10 mg/kg/day (N=32)
Subjects with clinically relevant response at Week 20 and at Week 24, n (%)	1 (6.3)	16 (45.7)	8 (25.0)
ANCOVA (on the rank) test, p-value[a]			
0.10 mg/kg/day GATTEX vs. Placebo	0.172		
0.05 mg/kg/day GATTEX vs. Placebo	0.005		
0.10 mg/kg/day GATTEX vs. 0.05 mg/kg/day GATTEX	0.053		
Subjects achieving at least a 1-day reduction in weekly PN/IV volume at Week 24, n (%)	4 (25.0)	11 (31.4)	3 (9.4)
ANCOVA (on the rank) test, p-value[b]			
0.10 mg/kg/day GATTEX vs. Placebo			0.120
0.05 mg/kg/day GATTEX vs. Placebo		0.684	
0.10 mg/kg/day GATTEX vs. 0.05 mg/kg/day GATTEX		0.031	
Actual change from baseline in PN/IV volume (L) at Week 24, Mean (±SD)	–0.90 (1.41)	–2.48 (2.34)	–2.47 (3.33)
Difference from placebo p-value[c]		0.0768	0.0755
Difference from 0.05 mg/kg/day GATTEX p-value[c]			0.9776

ANCOVA = analysis of covariance; N, n = number; PN/IV = parenteral nutrition/intravenous fluid; SD = standard deviation

a. Test Statistic is based on pairwise rank ANCOVA after adjustment for the baseline PN/IV consumption level and baseline PN/IV volume as a covariate. One subject was missing baseline and could not be ranked. Therefore, this subject was not included in the calculation of the test statistic for Rank ANCOVA 0.05 mg/kg/day – Placebo and 0.10 mg/kg/day – 0.05 mg/kg/day.

b. Test statistic is based on pairwise rank ANCOVA after adjustment for the baseline PN/IV consumption level and baseline PN/IV volume as a covariate.

c. A repeated measures model (Proc Mixed) was used with effects for treatment, visit, and treatment by visit interaction, and baseline PN/IV volume and baseline PN/IV consumption level as covariates.

Source: CSR Study 004, Tables 14.2.2.13, 14.2.2.15, 14.2.3.5.1, and 14.2.3.5.2

6.3.2.2 Achievement of at Least a One-Day Reduction in Weekly PN

A numerically higher proportion of subjects in the GATTEX 0.05 mg/kg/day group achieved at least a 1-day reduction in weekly PN/IV volume compared with placebo group, however the difference between the GATTEX group and placebo was not statistically significant (Table 13).

6.3.2.3 Absolute Change from Baseline in Weekly PN Kilojoules

Mean reductions from Baseline in weekly PN/IV kilojoules were observed in all 3 treatment groups at Week 24 and the Last Dose Visits, with the largest mean change in the GATTEX 0.05 mg/kg/day group. The reduction of energy infused was not different between placebo and either GATTEX dose group (CSR Study 004, Tables 14.2.3.15 and 14.2.3.17).

6.3.2.4 Change from Baseline in Weekly PN/IV Volume

At Week 24, a mean weekly PN/IV reduction of -2.5 L was observed in both active treatment groups compared to -0.9 L for placebo (p=0.08 for each comparison of active versus placebo) (Table 13).

6.3.2.5 48-Hour Oral Fluid Intake and Urinary Output

The 48-hour median oral intake (390 mL) and urine output (200 mL) were increased at Week 24 compared to Baseline in the placebo group (Table 14). In both active treatment groups, 48-hour median oral intake was decreased from Baseline at Week 24 (-95.0 mL in the low-dose group and -410 mL in the high-dose group) and 48-hour median urine output was increased from Baseline at Week 24 (420.0 mL in the low-dose group and 132.5 mL in the high-dose group).

Protocol constraints that likely affected these findings are discussed in Section 6.3.3.4.

Table 14. 48-Hour Oral Fluid Intake and Urinary Output – Study 004 (Intent-to-Treat Population)

Visit	Placebo (N=16)	GATTEX 0.05 mg/kg/day (N=35)	GATTEX 0.10 mg/kg/day (N=32)	GATTEX Total (N=67)
Baseline 48-hr oral (mL)				
N	13	31	30	61
Mean (SD)	4898.1 (3605.59)	3881.5 (1787.58)	4549.8, (1946.15)	4210.2, (1881.98)
Median	3570.0	3950.0	4460.0	4090.0
Min, Max	1230, 12550	730, 9650	1450, 9405	730, 9650
Week 24 change from Baseline 48-hr oral (mL)				
N	13	24	26	50
Mean (SD)	-99.3 (1735.04)	121.5 (1869.81)	-784.6 (1293.74)	-349.7 (1644.42)
Median	390.0	-95.0	-410.0	-175.0
Min, Max	-4261, 2400	-3340, 5990	-4570, 950	-4570, 5990
Baseline 48-hr urine (mL)				
N	13	29	30	59
Mean (SD)	3165.8 (454.74)	2793.8 (734.69)	3000.6 (1116.05)	2898.9 (945.64)
Median	3150.0	2800.0	2860.0	2800.0
Min, Max	2490, 4025	1675, 4860	1650, 7675	1650, 7675
Week 24 change from Baseline 48-hr urine (mL)				
N	13	23	26	49
Mean (SD)	232.2 (830.60)	733.7 (970.95)	-74.1 (1121.98)	305.1 (1119.66)
Median	200.0	420.0	132.5	310.0
Min, Max	-975, 1895	-500, 3740	-3900, 1450	-3900, 3740

N=number, Max=maximum, Min=minimum, SD=standard deviation
Source: CSR Study 004, Tables 14.2.2.29, 14.2.2.30, and 14.2.2.31

6.3.2.6 Change from Baseline in Plasma Citrulline at Week 24

A mean increase from Baseline in plasma citrulline was observed in all 3 treatment groups at Week 24, with those in the active treatment groups 5-fold (10.9 µmol/L in low-dose group) to 7-fold (15.7 µmol/L in high-dose group) greater than that with

placebo (2.0 µmol/L) ($p<0.001$ for each comparison between GATTEX dose group and placebo).

In related exploratory PK/PD analyses, no clear relationship between GATTEX AUC and plasma citrulline was observed at Week 24.

6.3.3 Exploratory Endpoints

6.3.3.1 Time to Events

Mean time in weeks to 20% reduction in weekly PN/IV volume was reduced significantly among the subjects treated with GATTEX 0.05 mg/kg/day compared to placebo (14.4 vs. 19.5 weeks, respectively; $p=0.0261$). No statistically significant differences were noted between the GATTEX 0.10 mg/kg/day (mean time to 20% reduction in weekly PN/IV volume = 18.8 weeks) and placebo groups.

The difference between the GATTEX 0.05 mg/kg/day and placebo groups in time to ≥ 1 day PN/IV reduction approached the level of statistical significance (mean of 17.8 vs. 20.8 weeks, respectively; $p=0.0867$), whereas there was no difference between the high-dose (21.8 weeks) and placebo groups (CSR Study 004, Table 14.2.3.19).

6.3.3.2 Change from Baseline to Week 24 Variables

6.3.3.2.1 Reduction in IV Catheter Access at Week 24

No statistically significant differences were noted for IV catheter access associated with infusion of PN/IV among treatment groups at Baseline, Week 24, and Last Dose Visit. Compared to Baseline, 55.6% (15/27) of subjects in GATTEX 0.05 mg/kg/day group and 44.8% (13/29) of subjects in the GATTEX 0.10 mg/kg/day group vs. 31.3% (5/16) of subjects in the placebo group had reduced IV catheter access at Week 24. Similar results were obtained for the Last Dosing Visit. (CSR Study 004, Table 14.2.7.1).

6.3.3.3 Actual and Prescribed PN/IV

A comparison of the absolute and percent (%) differences between actual and prescribed weekly PN/IV volumes showed similar results for the treatment groups at Baseline, Week 24, Last Dose Visit, Change from Baseline to Week 24, and Change from Baseline to Last Dose Visit (CSR Study 004, Table 14.2.3.9 to Table 14.2.3.12).

6.3.3.4 Fluid Composite Effect (FCE)

Clinically, the extent of absorption corresponds to the difference between fluid intake (oral + PN/IV) and output (urinary and stool). In Study 92001, oral and PN/IV fluid intake could be fixed so that changes in output reflected changes in absorptive capacity. GATTEX caused a direct increase in urine output and a decrease in fecal wet weight (decrease in fluid loss in stool) that allows an increase in urine output to be a marker of increased absorption (given stable input). Note: FCE = change PN/IV volume + change oral volume – change in urine volume (L/week).

In Study 004 the mean weekly reduction in the fluid composite effect at Week 24 was significantly greater in the GATTEX 0.05 mg/kg/day treatment group (-5.22 L/week) compared with placebo (p=0.017).

6.3.3.5 Quality of Life

The overall results from 3 QOL assessments (SF-36, EuroQol EQ-5D, and IBDQ) indicated no major treatment effect, as compared to placebo, on QoL parameters after 24 weeks of treatment (CSR 004, Tables 14.2.6.1 to 14.2.6.38).

6.3.3.6 Mucosal Crypt-Villus Architecture and Cellular Composition Within the Small and Large Intestine

GATTEX administration induced significant structural adaptations in the intestinal mucosa of adult subjects with SBS, as previously discussed in Section 4.3. Both GATTEX doses induced expansion of the absorptive epithelium by increasing villus height in the small intestine (GATTEX 0.05 mg/kg/day [p=0.0065] and GATTEX

0.10 mg/kg/day [p=0.0024]). The composition of the GATTEX mucosa did not differ from placebo when expressed on a mucosal mass basis, indicating that these structural adaptations involved the production of additional tissue that did not differ in cellular size or composition from what was originally present. Histopathological evaluation of the intestinal tissue samples demonstrated no development of dysplastic changes.

6.4 Conclusions from Study 004

GATTEX treatment reduced the need for PN/IV among PN/IV dependent SBS adults during this 24-week study via its effects on function and anatomy, with clinically significant separation from placebo at the lower 0.05 mg/kg/day dose. A mean 2.5 L/week reduction from Baseline in PN/IV volume was achieved in both GATTEX dose groups at Week 24. Secondary and exploratory analyses of the 0.05 mg/kg/day dose also supported clinically significant decrease in PN/IV fluids. Both the 0.10 mg/kg/day and 0.05 mg/kg/day dose groups had increased villous height and other changes, suggesting significant pharmacodynamic effect. Two subjects (of the 16 responders) in the 0.05 mg/kg/day group were completely weaned off PN/IV during the 24 weeks of GATTEX treatment, 1 having been on PN/IV for approximately 25 years, and the other, for 6.5 years. One subject in the 0.10 mg/kg/day group, who had been on PN/IV for 3.7 years, discontinued PN/IV at Week 24.

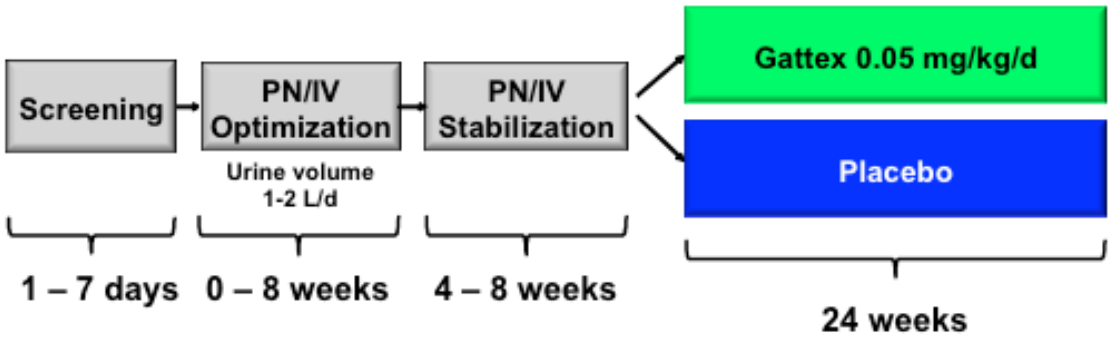
In exploratory analyses to evaluate the success of the weaning algorithm, both GATTEX dose groups achieved a similar clinically and statistically significant difference from placebo with respect to the fluid composite effect. The substantial increase in oral fluid intake first recorded at Week 4 suggests an early onset of effect with GATTEX. Had the protocol allowed for earlier and more substantial PN/IV volume reduction (rather than restricting first reduction to 4 weeks after start of drug), oral fluid intake likely would have remained constant and the mean reduction in PN/IV volume likely greater than the observed 2.5 L/week value for both GATTEX groups. Accordingly, Study 020 allowed for more flexible investigator reduction in PN/IV fluids.

7.0 Efficacy Findings in Study 020

7.1 Study Design

Study 020 was a randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter study. The study was comprised of 2 stages (Figure 17): Stage 1 included a screening visit, an optimization period of up to 8 weeks, and a 4- to 8-week stabilization period of up to 8 weeks (that was designed to demonstrate stable administration of PN/IV for a minimum of 4 weeks that could be utilized to establish Baseline). The optimization and stabilization scheme for Study 020 was identical to that used in Study 004, as previously described (Section 6.1).

Figure 17. Study Design – Study 020



PN/I.V.= Parenteral nutrition/intravenous fluid.
Source: CSR Study 020

Once subjects had successfully completed the optimization and stabilization period (Stage 1), demonstrating PN/IV volume stability for 4 to 8 weeks, Stage 2 of the study began with baseline assessments of hydration and nutritional status. These subjects were randomized in a 1:1 ratio to either placebo or GATTEX 0.05 mg/kg/day. Randomization was stratified by PN/IV consumption level at baseline (≤6 L/week, >6 L/week). The GATTEX dose calculation was based on the average of 2 separate measures of body

weight after stabilization. GATTEX or matching placebo was administered by SC injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.

After 86 subjects were randomized, there was no further randomization. However, subjects who were still in Stage 1 of the study were given the choice to either immediately terminate participation in the study or continue through the optimization (if necessary) and stabilization period (minimum of 4 weeks, maximum of 8 weeks). The subjects who completed the stabilization period and were eligible to be randomized into the study were given the choice to enter directly into the 24-month long-term safety study (Study 021) without entering Stage 2 of Study 020.

All subjects measured PN/IV volumes on a daily basis between the clinical visits, recording the values in electronic diaries. Subjects also measured 48-hour oral fluid intake and 48-hour urine output at home immediately prior to the scheduled visit.

During the treatment phase (Stage 2), decisions about whether to adjust PN/IV volume were made at dosing Weeks 2, 4, 8, 12, 16, and 20. To preserve blinding, the person responsible for decisions about adjusting PN/IV volume was different from the person conducting physical examinations and assessing safety.

As mentioned earlier, observations in Study 004 led to changes in the PN/IV volume reduction algorithm for Study 020 (differences summarized in Section 5.1.2). Subject's PN/IV volume was adjusted based on guidance suggested in the protocol: PN/IV volume was increased if urine output was less than 1.0 L/day and decreased if urine output had increased by at least 10% from baseline. Reductions in PN/IV volume were between 10% and 30% of the stabilized baseline PN/IV level. (PN/IV volume adjustments outside the guidance were allowed, if deemed medically necessary.) The protocol also stipulated that oral fluid intake during the 48-hour urine output measurement period should be consistent with oral fluid intake at baseline.

Interim safety evaluations were performed 5-7 days after any scheduled visit when a reduction was made to the subject's PN/IV. These measures included 48-hour oral fluid

intake, 48-hour urine output, hematocrit, BUN, creatinine, and urine sodium. The exception was the Visit 4/Week 2 interim safety visit, when a phone call was made to assess if the PN/IV adjustment was tolerated.

7.1.1 Subject Population – Selection and Exclusion Criteria

Approximately 140 subjects were to be screened to provide about 86 randomized subjects.

Inclusion Criteria

This study was to enroll subjects who meet the following criteria:

1. Signed and dated ICF before any study-related procedures are performed
2. Men and women, 18 years of age or older at the time of signing the ICF
3. Intestinal failure resulting in SBS as a consequence of major intestinal resection (e.g., due to injury, volvulus, vascular disease, cancer, Crohn's disease)
4. For subjects with a history of Crohn's disease, the subject must have been in clinical remission for at least 12 weeks prior to dosing as demonstrated by clinical assessment, which may have included procedure-based evidence of remission
5. Subjects who had undergone intestinal resection resulting in at least 12 continuous months of dependency on PN/IV fluid prior to signature of ICF
6. PN/IV fluid required at least 3 times per week during the week before screening and during the 2 weeks prior to baseline to meet their caloric, fluid, or electrolyte needs due to ongoing malabsorption
7. Stable PN/IV volume for at least 4 consecutive weeks immediately prior to randomization based upon the opinion of the investigator and approval by the sponsor's Medical Monitor. Stability was described as:
    a. Actual PN/IV fluid usage should match prescribed PN/IV volume
    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes should fall within ± 25% of the respective 48-hour I/O volumes at the time the subject was optimized and entered stabilization
    c. Urine output volume should NOT have fallen below 2 L and not have exceeded 4 L per 48 hours when the subject completed the optimization and stabilization periods

Exclusion Criteria

Subjects who met any of the following criteria were excluded:

1. History of cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state. This did not include resected cutaneous basal or squamous cell carcinoma, or in situ non-aggressive and surgically resected cancer
2. Participation in a clinical study using an experimental drug within 30 days or an experimental antibody treatment within 90 days prior to signing the ICF, or concurrent participation in any clinical study using an experimental drug.
3. Previous use of native GLP-2 or human growth hormone within 6 months prior to screening
4. Previous use of IV glutamine, octreotide, GLP-1 analog, or DDP-IV inhibitors within 30 days prior to screening
5. Previous use of GATTEX
6. Subjects with Crohn's disease who had been treated with biological therapy (e.g., anti-tumor necrosis factor or natalizumab) within the 6 months prior to screening
7. Subjects with IBD who required chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months
8. More than 4 SBS-related or PN-related hospital admissions (e.g., catheter sepsis, bowel obstruction, severe water-electrolytes disturbances) within 12 months prior to screening visit
9. Hospital admission, other than scheduled, within 1 month prior to screening
10. Pregnant or lactating women
11. Body weight >88 kg
12. Body mass index (BMI) ≤15 kg/m^2
13. Signs of severe hepatic impairment or disturbed renal function:
    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. For subjects with Gilbert's disease, direct (conjugated) bilirubin ≥2xULN.
    c. Aspartate aminotransferase (AST) ≥5xULN
    d. Serum creatinine ≥2xULN
14. Female subjects who were not surgically sterile or postmenopausal (defined as aged 55 years or older and/or at least 2 years had elapsed since her last menses) or who were not using medically acceptable methods of birth control during and for 30 days after the treatment period
15. Not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements

16. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results
17. Presence of any of the excluded disease states described in the table below:

Excluded Diseases and Illnesses

Body system	Conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis; celiac disease; refractory or tropical sprue; pseudo-obstruction
Gastrointestinal	Active IBD which required chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months; IBD that required chronic systemic immunosuppressant therapy for symptom control; untreated pre-malignant or malignant change in colonoscopy biopsy or polypectomy; intestinal or other major surgery scheduled within the time frame of the study; chronic pancreatitis or cholecystitis
Immune	Compromised immune system (e.g., acquired immune deficiency syndrome, severe combined immunodeficiency); hypersensitivity or allergies to GATTEX or its constituents or GLP-2
Psychiatric	Alcohol or drug addiction within the previous year; major uncontrolled psychiatric illness
General	Significant active, uncontrolled, untreated systemic diseases (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

7.1.2 Definitions of Efficacy Endpoints

7.1.2.1 Primary Endpoint

The primary efficacy variable was the percentage of subjects who demonstrated a response at Week 20 and at Week 24 (responder). A response was defined as the achievement of a 20% to 100% reduction from baseline in weekly PN/IV volume (also referred to as a "clinically relevant response"). The weekly PN/IV volume was defined using data from the last 14 days prior to the visit.

7.1.2.2 Secondary Endpoints

The secondary efficacy variables were based on reductions in PN/IV volume. The secondary variables were to include:

- percent change and absolute change in PN/IV volume between Baseline and last dosing visit;
- duration of response (number of consecutive visits with a 20 to 100% PN/IV volume reduction immediately preceding a response at Week 24);
- the proportion of subjects with 20 to 100% reduction or a ≥ 2 L reduction from Baseline in weekly PN/IV volume at Week 20 and at Week 24;
- the number of subjects who stop (were able to wean from) PN/IV fluid and time of discontinuation.
- an ordered categorical (or graded) response that accounted for both intensity and duration of the response at the end of the 24-week treatment period. The intensity of the response relies on a reduction from Baseline in weekly PN/IV volume at a minimum of 20% and a maximum of 100%. Duration of the response incorporates responses at Weeks 16, 20, and 24.

7.1.2.3 Exploratory Endpoints

Exploratory efficacy endpoints included response (a 20 to 100% reduction from baseline in weekly PN/IV volume) by visit, reduction in number of days with PN/IV infusion, and the fluid composite effect (to measure changes in intestinal absorption). The fluid composite effect was calculated at Baseline and at each dosing visit as changes in PN/IV Volume (L/week) + Oral Fluid Intake (L/week) – Urine Output (L/week). The fluid composite effect was not calculated for any post-baseline visit where at least 1 of the 3 contributing variables was not collected. A newly developed subject-reported outcome SBS-specific QoL questionnaire (SBS-QoL™) was validated and subsequently used in

this study to assess the burden of various aspects of PN/IV dependence and SBS and to evaluate the subject's QoL.

7.1.2.4 Sample Size and Powering

Eighty-six subjects were randomized at a 1:1 ratio to detect a difference in responder rates between GATTEX and placebo groups of 35% and 6%, respectively, α alpha=0.05, 2-sided test, and power=90%. Grounded on these assumptions, nQuery Advisor (v. 6.0) based on a Fisher's Exact Test was used to calculate the power.

7.1.2.5 Analysis Populations

The ITT population included all subjects who were randomized into the study. All efficacy analyses were conducted on this study population. Subjects were included in the treatment group to which they were randomized, regardless of the actual drug they received.

The Safety population included all subjects in the ITT population who received at least 1 dose of double-blind study drug. Subjects were included in the treatment group reflective of the treatment they actually received.

7.1.2.6 Analysis of Primary Endpoint

The primary analysis compared the response rates for the 2 treatment groups using Cochran Mantel-Haenszel test statistics adjusted for the randomization stratification variable (≤6 or > 6 L/week of PV/IV at Baseline).

7.1.2.7 Analysis of Secondary Endpoints

All categorical secondary endpoints were analyzed in a similar fashion to the primary endpoint. Continuous secondary endpoints were analyzed using analysis of variance (ANOVA) incorporating treatment effects and continuous measures corresponding to stratification variables. Secondary efficacy parameters were hierarchically tested.

7.1.2.8 Subgroup Analyses of Efficacy

The primary and selected secondary efficacy parameters were presented for the ITT population by each of the following subgroups:

- country
- gender
- age category (<45, 45-<65, ≥65 years)
- colon-in-continuity (Y/N)
- ileo-cecal valve (Y/N)
- presence of stoma (Y/N)
- race
- randomization stratification variable (≤6 L/week, >6 L/week)

7.1.2.9 Sensitivity Analyses

A description of the sensitivity analyses conducted and summary of the results are presented in Appendix A.

7.2 Subject Disposition, Demographics, Other Baseline Characteristics, and Concomitant Medications Taken During the Study

7.2.1 Subject Disposition

A total of 136 subject numbers were assigned to Study 020. However, 4 subjects were screened twice (i.e., under 2 separate subject numbers), thus only 132 unique subjects were screened for participation in this study, of whom 86 were randomized from 27 centers (US 6, Canada 4, Poland 4, Germany 2, Italy 3, France 2, Spain 2, United Kingdom 2, Denmark 1, Netherlands 1) in 10 countries. No subject was randomized more than once. Of the remaining 46 subjects, 34 subjects were considered screen failures. The 12 additional subjects were eligible for randomization. However, because randomization had been completed they were allowed to directly enter the long-term safety study (Study 021).

Of the 86 subjects randomized, 78 completed the study and 8 discontinued from the study during the dosing period, including 1 subject who was randomized but did not receive study drug. The specific reasons for discontinuation are summarized in Table 15. Two subjects in the GATTEX group and 3 subjects in the placebo group discontinued due to a treatment-emergent AE.

Table 15. Subject Disposition – All Subjects Screened for Study 020

Category	Placebo	GATTEX 0.05 mg/kg/day	All Subjects
Randomized, n	43	43	86
Treated, n	43	42[a]	85
Completed dosing period, n (%)	39 (90.7)	39 (90.7)	78 (90.7)
Discontinued during dosing period, n (%)	4 (9.3)	4 (9.3)	8 (9.3)
Subject decision	1 (2.3)	0	1 (1.2)
Lost to follow-up	0	0	0
Adverse event	3 (7.0)	2 (4.7)	5 (5.8)
Investigator decision	0	1 (2.3)	1 (1.2)
Death	0	0	0
Other	0	1 (2.3)	1 (1.2)

a. One subject in the GATTEX group was excluded from the Safety population because the subject was randomized in error (site test of the IVRS system) and was not dispensed any dose of double-blind study drug.

Note: Percentages for the Screening, Optimization, and Stabilization Periods were based on the number of subjects screened. Percentages for the Dosing Period were based on the number of subjects randomized.
Source: CSR Study 020, Table 14.1.1.1

The ITT analysis population included all 86 subjects who were randomized: 43 to placebo and 43 to GATTEX 0.05 mg/kg/day. One subject was randomized in error by the investigator to GATTEX in order to test the interactive voice response system (IVRS). The subject was per definition included in the ITT population but was discontinued from the study prior to receipt of study drug because of failure to obtain a stabilized PN/IV level.

Disposition of subjects in the Safety population is provided in Section 9.2. A total of 85 subjects received at least 1 dose of study drug and comprise the Safety population. One subject (in the GATTEX group) of the 86 randomized subjects was excluded from the Safety population because the subject was randomized in error (site test of the IVRS system) and was not dispensed any dose of double-blind study drug.

7.2.2 Demographic Characteristics

In general, baseline demographic data were similar between the GATTEX 0.05 mg/kg/day and placebo treatment groups (Table 16). The majority of subjects enrolled in this study were Caucasian (83/86 subjects, 96.5%). Given a lack of rationale for mechanistic differences by race, the results are generalizable to the SBS population at large. Mean (SD) age was 50.3 (14.1) years, with 15.1% (13/86 subjects) ≥65 years of age. The population was 46.5% male (40/86 subjects). There were no statistically significant differences between treatment groups based on demographic characteristics.

Table 16. Demographics Characteristics – Study 020 (Intent-to-Treat Population)

Parameter	Placebo (N=43)	GATTEX 0.05 mg/kg/day (N=43[a])	All Subjects (N=86)
Age at informed consent (years)			
Mean (SD)	49.7 (15.6)	50.9 (12.6)	50.3 (14.1)
Min, Max	18, 82	22, 78	18, 82
p-value		0.694	
Gender, n (%)			
Male	19 (44.2)	21 (48.8)	40 (46.5)
Female	24 (55.8)	22 (51.2)	46 (53.5)
p-value		0.829	
Race, n (%)			
White	41 (95.3)	42 (97.7)	83 (96.5)
Black	1 (2.3)	0	1 (1.2)
Asian	1 (2.3)	1 (2.3)	2 (2.3)
Ethnicity, n (%)			
Hispanic or Latino	4 (9.3)	5 (11.6)	9 (10.5)
Not Hispanic or Latino	39 (90.7)	38 (88.4)	77 (89.5)
Baseline PN/IV randomization stratification, n (%)			
≤6 L/week	7 (16.3)	8 (18.6)	15 (17.4)
>6 L/week	36 (83.7)	35 (81.4)	71 (82.6)
Body weight at baseline (kg)			
Mean (SD)	61.70 (12.61)	62.74 (11.41)	62.21 (11.97)
Min, Max	40.9, 86.0	43.4, 87.9	40.9, 87.9
p-value		0.691	
BMI at baseline (kg/m^2)			
Mean (SD)	22.25 (3.12)	22.46 (3.19)	22.35 (3.14)
Min, Max	17.5, 28.6	17.6, 29.8	17.5, 29.8
p-value		0.759	

a. N = 42 for weight and BMI.

BMI=body mass index, PV/IV=intravenous parenteral nutrition.

Note: The treatment comparisons for continuous variables are based on an ANOVA model with treatment as an effect. The treatment comparisons for gender are based on Fisher's Exact Test.

Source: CSR Study 020, Table 14.1.3.2

7.2.3 Other Baseline Characteristics

The SBS history for the Safety population is summarized in Table 17. The most prevalent causes for major intestinal resection were vascular disease (29/85 subjects, 34.1%), Crohn's (18/85 subjects, 21.2%), or "other" reason (18/85 subjects, 21.2%). Stoma was present in 38 of 85 subjects (44.7%), with the most common types being jejunostomy/ileostomy (31/38 subjects, 81.6%). The mean length ± SD of the remaining small intestine was 77.3±64.4 cm (range: 5 to 343 cm). The length of small intestine was clinically comparable for subjects in the GATTEX group (86.2 cm) compared with the placebo group (68.7 cm).

The colon was not in continuity in 37 of 85 subjects (43.5%). Forty-eight of 85 subjects (56.5%) had some degree of colon in continuity. For subjects with any colon, a mean of 63.1% of colon remained in these subjects. Subjects in the placebo group had a higher numerical percentage of mean colon remaining (70.3%) than the GATTEX group (55.6%). Of the 24 subjects with remaining distal/terminal ileum, the ileocecal valve was present in 13 subjects (54.2%).

Table 17. Short Bowel Syndrome History – Study 020 (Safety Population)

Parameter	Placebo (N=43)	GATTEX 0.05 mg/kg/day (N=42)	All Subjects (N=85)
Reason for major intestinal resection, n (%)			
N	43	42	85
Crohn's disease	8 (18.6)	10 (23.8)	18 (21.2)
Vascular disease	16 (37.2)	13 (31.0)	29 (34.1)
Injury	4 (9.3)	4 (9.5)	8 (9.4)
Volvulus	6 (14.0)	3 (7.1)	9 (10.6)
Cancer	2 (4.7)	1 (2.4)	3 (3.5)
Other	7 (16.3)	11 (26.2)	18 (21.2)
Stoma			
N	43	42	85
Yes	17 (39.5)	21 (50.0)	38 (44.7)
No	26 (60.5)	21 (50.0)	47 (55.3)
Type of stoma			
N	17	21	38
Jejunostomy	5 (29.4)	11 (52.4)	16 (42.1)
Ileostomy	9 (52.9)	6 (28.6)	15 (39.5)
Colostomy	1 (5.9)	4 (19.0)	5 (13.2)
Other	2 (11.8)	0	2 (5.3)
Colon-in-continuity			
N	43	42	85
Yes	23 (53.5)	25 (59.5)	48 (56.5)
No (includes no colon)	20 (46.5)	17 (40.5)	37 (43.5)
Percent of colon remaining			
N	25	24	49
Mean (SD)	70.3 (27.1)	55.6 (20.8)	63.1 (25.1)
Min, Max	10, 100	20, 100	10, 100
Estimated remaining small intestine length (cm)			
N	40	39	79
Mean (SD)	68.7 (63.9)	86.2 (64.5)	77.3 (64.4)
Min, Max	5, 343	20, 250	5, 343
<60 cm	24 (55.8)	15 (35.7)	39 (45.9)
≥60 cm	16 (37.2)	24 (57.1)	40 (47.1)

Table 17. Short Bowel Syndrome History – Study 020 (Safety Population) (Continued)

Parameter	Placebo (N=43)	GATTEX 0.05 mg/kg/day (N=42)	All Subjects (N=85)
Presence of distal/terminal ileum, n (%)			
N	43	42	85
Yes	14 (32.6)	10 (23.8)	24 (28.2)
No	29 (67.4)	32 (76.2)	61 (71.8)
Presence of ileocecal valve, n (%)			
N	14	10	24
Yes	10 (71.4)	3 (30.0)	13 (54.2)
No	4 (28.6)	7 (70.0)	11 (45.8)
Methodology for determining length of remaining anatomy, n (%)			
N	42	41	83
Surgery	34 (81.0)	35 (85.4)	69 (83.1)
Radiology	6 (14.3)	4 (9.8)	10 (12.0)
Other	2 (4.8)	2 (4.9)	4 (4.8)

Note: Questions for type of stoma and presence of ileocecal valve were only relevant when a distal/terminal ileum was present. Percent of colon remaining was only relevant when the subject had a colon.

Source: CSR Study 020, Table 14.1.5.1

Table 18 summarizes parenteral support at Baseline. The mean (±SD) prescribed weekly PN/IV volume at Baseline was 12.87 L (±7.57). Mean prescribed days/week requiring PN/IV infusion was 5.73 (±1.59) days. Most of the subjects (75/85, 88.2%) had subclavian central venous IV access.

Table 18. Parenteral Support Status at Baseline – Study 020 (Safety Population)

Parameter	Placebo (N=43)	GATTEX 0.05 mg/kg/day (N=42)	All Subjects (N=85)
Prescribed weekly PN/IV volume (L)			
Mean (SD)	13.29 (7.54)	12.44 (7.67)	12.87 (7.57)
Min, Max	2.4, 34.3	0.9, 33.0	0.9, 34.3
Actual weekly PN/IV volume (L)			
Mean (SD)	13.37 (7.40)	12.45 (7.75)	12.92 (7.55)
Min, Max	2.4, 34.3	0.9, 33.1	0.9, 34.3
Prescribed weekly number of days of PN/IV			
Mean (SD)	5.91 (1.54)	5.55 (1.64)	5.73 (1.59)
Min, Max	3.0, 7.0	3.0, 7.0	3.0, 7.0
Actual weekly number of days of PN/IV			
Mean (SD)	5.98 (1.43)	5.58 (1.57)	5.78 (1.50)
Min, Max	3.0, 7.0	3.0, 7.0	3.0, 7.0

PN/IV=parenteral nutrition/intravenous.
Source: CSR Study CL0600-020, Table 14.1.6.2

With regard to medical and surgical history, the most frequently reported were GI disorders (GATTEX 40/42 subjects, 95.2%; placebo 41/43 subjects, 95.3%) and infections and infestations (GATTEX 25/42 subjects, 59.5%; placebo 23/43 subjects, 53.5%).

7.2.4 Concomitant Medications Taken During the Study

The majority of subjects reported having taken at least 1 concomitant medication during their participation in the study (41/42, 97.6% GATTEX subjects and 41/43, 95.3% placebo subjects). The most frequently reported concomitant medications (≥15% in either treatment group) were proton pump inhibitors (esomeprazole, omeprazole, and pantoprazole) and antipropulsives (loperamide) (CSR Study 020, Table 14.1.8.2).

7.3 Findings in Study 020

7.3.1 Primary Efficacy Endpoint

The results of the primary efficacy analysis from Study 020 are summarized in Table 19. The proportion of subjects with a clinically relevant response at Week 20 and at Week 24 (responders) was significantly greater in the GATTEX group compared with the placebo group (62.8% vs. 30.2%; p=0.002).

Table 19. Responder Rate – Study 020 (Intent-to-Treat Population)

Response Status	Placebo (N = 43) n (%)	GATTEX 0.05 mg/kg/day (N= 43) n (%)
Non-responder	30 (69.8)	16 (37.2)
Responder	13 (30.2)	27 (62.8)
p-value	0.002	

N, n = number

Note: Percentages are based on the number of subjects in the Intent-to-Treat Population. Note: Responder is defined as a subject who achieves a clinically relevant response (i.e., a reduction of 20% to 100% in PN/IV volume from baseline) at Week 20 and at Week 24. The treatment comparison is based on a Cochran-Mantel-Haenszel test adjusted for the randomization stratification variable.

Source: CSR Study 020, Table 14.2.1.1

7.3.1.1 Subgroup Analyses of Primary Endpoint

Results across subgroup analyses were consistent with the primary endpoint results, with substantial treatment benefit with GATTEX compared to placebo in all subgroup analyses (CSR Study 020, Tables 14.2.1.3 – 14.2.1.9). Due to small subject numbers within the subgroups, the numerical between-group differences were not the same.

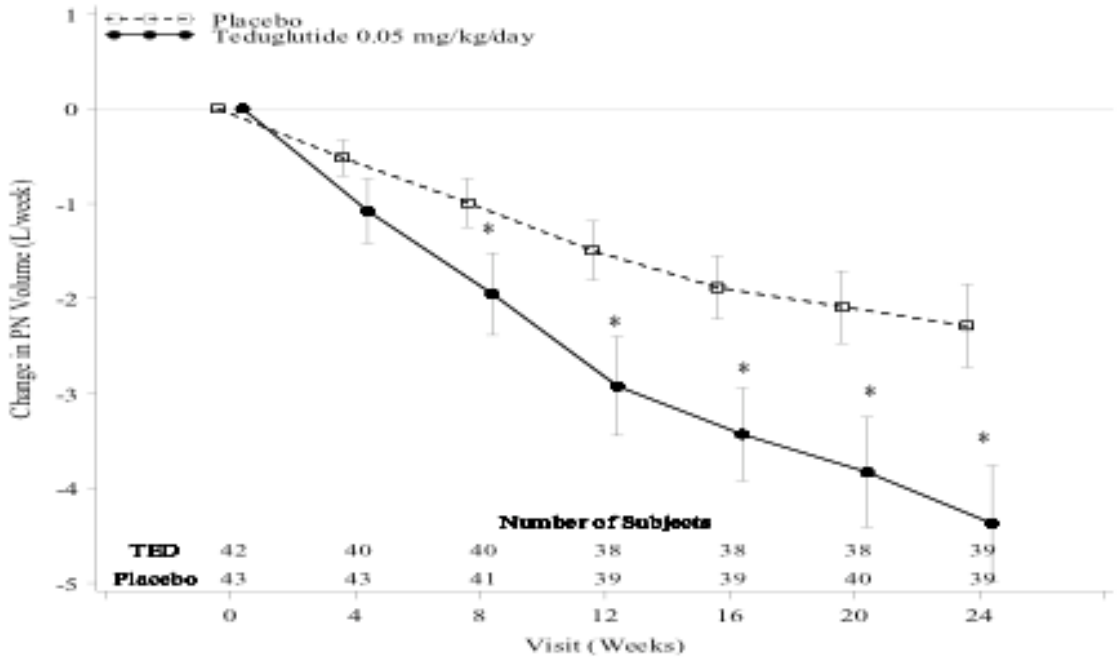
7.3.1.2 Sensitivity Analyses of the Primary Endpoint

Results of the primary analysis are supported by multiple sensitivity analyses. The sensitivity analyses assessed the impact of missing data, based upon cases where a scheduled visit after Week 2 was either not conducted, the weekly PN/IV volume could not be calculated for the preceding 14 days, or there was at least one of the preceding 14 days where a PN/IV value was not provided in the diary (results presented in Table 31, Appendix A).

7.3.2 Secondary Efficacy Endpoints

At all visits, subjects treated with GATTEX had greater absolute change (Figure 18) from Baseline in actual PN/IV volume compared to placebo subjects. The clinical effect for subjects was seen as early as Week 2, with a statistically significant between-group difference starting at Week 8 and Week 12, respectively, and continuing through Week 24. Of note, any adjustment seen in a subject's diary reflected the 14 days prior and a change in PN/IV that was prescribed at prior visit (e.g., for Week 4 this was a change in prescribed volume at Week 2). The absolute change from baseline with GATTEX was about twice that of placebo at all visits (-4.4 vs. 2.3 L/week, respectively, at Week 24, $p<0.001$).

Figure 18. Absolute Change in PN/IV Volume (L/week ± SE) – Study CL0600--020 (Intent-to-Treat Population)



L=liter; PN=parenteral nutrition, SE=standard error, TED=teduglutide
* $p < 0.05$
Source: CSR Study 020, Table 14.2.2.1

Key secondary endpoints of Study 020 are summarized in Table 20. At Week 24, mean absolute change from Baseline in PN/IV volume in the GATTEX group was -4.4 L/week from a baseline of 12.9 L/week and in the placebo group was -2.3 L/week from a Baseline of 13.2 L/week ($p<0.001$).

Table 20. Summary of Key Secondary Endpoints – Study 020 (Intent-to-Treat Population)

	Placebo (N = 43)	GATTEX 0.05 mg/kg/day (N= 43)	p-value
Absolute change from baseline in PN/IV volume at Week 24, Mean (±SD)	-2.29 (2.74)	-4.37 (3.81)	<0.001[a]
Percent change from baseline in PN/IV volume at Week 24, Mean (±SD)	-21.33 (25.43)	-32.42 (18.86)	0.017[a]
Subjects achieving a clinically relevant response by duration, n (%)			0.005[b]
0 visits	25 (58.1)	13 (30.2)	
1 visit	5 (11.6)	3 (7.0)	
2 visits	1 (2.3)	3 (7.0)	
≥3 visits	12 (27.9)	24 (55.8)	
Subjects with 20% or 2-liter reduction from Baseline in PN/IV volume at Week 20 and at Week 24, n (%)	16 (37.2)	30 (69.8)	0.002[c]
Subjects who stopped PN/IV as of Week 24, n (%)	1[d] (2.3)	0	>0.999[e]
Grade Response[f] Total Score, n (%)			0.004[b]
0	30 (69.8)	16 (37.2)	
1	1 (2.3)	3 (7.0)	
2	6 (14.0)	13 (30.2)	
3	2 (4.7)	4 (9.3)	
4	4 (9.3)	7 (16.3)	
5	0	0	

N, n=number, PN/IV=parenteral nutrition/intravenous fluids, SD=standard deviation

a. Based on an ANCOVA model with treatment and interaction of treatment by baseline PN/IV volume as effects and baseline PN/IV volume as a covariate. b. Based on an extended Cochran-Mantel-Haenszel test with standardized midranks adjusted for the randomization stratification variable. c. Based on a Cochran-Mantel-Haenszel test adjusted for the randomization stratification variable. d. Subject stopped PN/IV during the 14 days prior to Week 24 according to the e-diary. This subject was not considered successful in weaning off PN/IV infusion since it was only temporarily interrupted due to hospitalization and catheter replacement (the implanted catheter was not working) immediately prior to Week 24. PN/IV infusion was provided to this subject both before and after the episode of catheter malfunction. During this time, the subject was not on PN/IV and the subject's weight progressively decreased (-4 kg). Parenteral nutrition was subsequently resumed. e. Based on an exact Chi-square test. f. The graded response accounts for intensity and duration of the response at Week 24. The intensity of the response at a visit relies on a 20-100% reduction from Baseline in weekly PN/IV volume. The duration of the response at a visit incorporates responses at Weeks 16 through 20 and at Weeks 20 through 24. Source: CSR Study 020, Tables 14.2.2.1, 14.2.2.11, 14.2.2.21, 14.2.2.31, 14.2.2.33

Duration of response was statistically significantly longer for GATTEX-treated subjects (p=0.005): 56% (24/43 subjects) achieved a clinically meaningful response for ≥3 consecutive visits (i.e., a response at least at Weeks 16, 20, and 24), as compared to 28% (12/43) of placebo subjects.

A higher proportion of GATTEX-treated subjects were responders, when defined as those achieving a 20 to100% reduction or 2 L reduction in PN/IV volume at Week 20 and at Week 24 (70% vs. 37% of placebo subjects; p=0.002).

No subjects were considered to have completely weaned off their PN/IV fluid at the end of the study. One placebo subject had stopped PN/IV fluid during the 14 days prior to Week 24 however, this subject was not considered successful in weaning off PN/IV support since PN/IV was only temporarily interrupted due to hospitalization and catheter replacement (the implanted catheter was not working) immediately prior to Week 24. PN/IV support was provided to this subject both before and after the episode of catheter malfunction.

7.3.3 Exploratory Endpoints

7.3.3.1 Logistic Regression of the Primary Efficacy Parameter

Logistic regression analysis was performed on the binary primary efficacy parameter utilizing the baseline PN/IV volume as a covariate. The results were consistent with the primary analysis (p=0.002 for GATTEX vs. placebo) (CSR Study 020, Table 14.2.3.1).

7.3.3.2 Reduction in Days of PN/IV Volume Per Week

Weekly PN/IV support at Week 24 was reduced by 1 or more days in those who completed the trial in over half of subjects in the GATTEX group (53.8% [21/39 subjects]) vs. 23.1% (9/39) of placebo subjects (p=0.005) (CSR Study 020, Table 14.2.3.3). In order to more fully explore the magnitude of the additional days off PN/IV support, post hoc analyses were conducted looking at 2 and ≥3 or more additional days off per week. It was determined that 8 (of 39, 21%) GATTEX-treated subjects

required 2 fewer days per week of PN/IV support, compared to 3 (of 39, 8%) placebo subjects and 4 (of 39, 10%) GATTEX-treated subjects required ≥3 fewer days per week of PN/IV support, compared to 2 (of 39, 5%) of placebo subjects.

7.3.3.3 Reduction from Baseline of 20% to 100% in Prescribed Weekly PN/IV

The proportion of responders based on prescribed PN/IV volume data was significantly greater in the GATTEX group than in the placebo group (62.8% [27/43 subjects] vs. 37.2% [16/43 subjects], respectively) (CSR Study 020, Table 14.2.3.4). These results support the responder conclusions based on the actual PN/IV volume data.

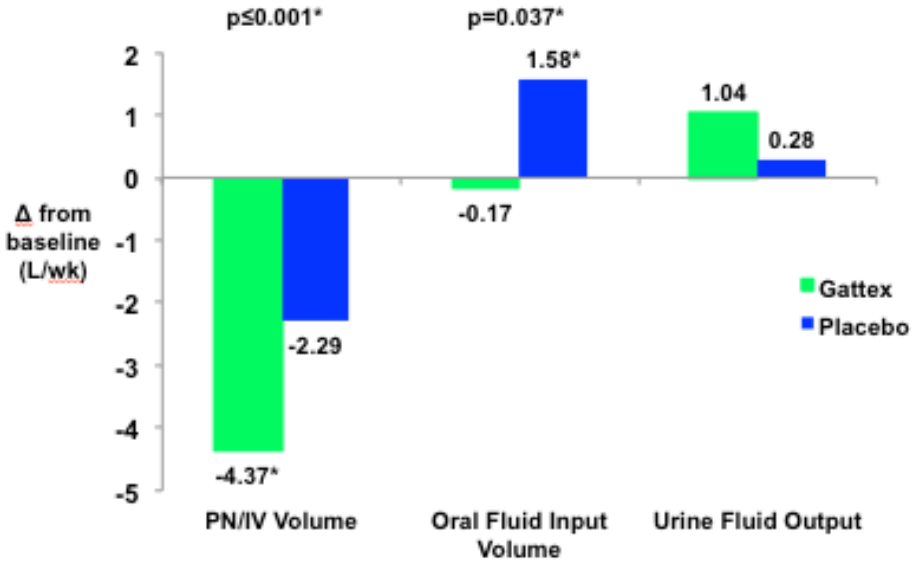
7.3.3.4 Absolute Change in Prescribed PN/IV Volume

At all visits, the absolute change from Baseline in the GATTEX group was about twice that in the placebo group at all visits (CSR Study 020, Table 14.2.3.5). These results support the conclusions for the change based on the actual PN/IV volume data.

7.3.3.5 Opportunity for Further PN/IV Volume Reduction Beyond Week 24

In the setting of stable oral intake and PN/IV volume reduction with GATTEX, urine output continued to increase (results at Week 24 shown in Figure 19) indicating increased net fluid absorption. Even at the end of the trial, further weaning appeared possible in subjects treated with GATTEX (based on their increased urine output).

Figure 19. PN/IV Reductions With GATTEX vs. Placebo at Week 24 – Study 020



7.3.4 Quality of Life Assessment

Health-related QoL was assessed as an exploratory endpoint in 020 using a subject-reported SBS-specific QoL scale (SBS-QoL™), which was designed in an attempt to measure QoL changes over time. Of note, this was the first clinical study to utilize the SBS-QoL™, and the study was not sized for this endpoint. The SBS-QoL tool was developed to look at various aspects of PN dependence in the SBS population.

QoL data showed that PN volume reduction was correlated to QoL scores in SBS patients but the difference did not reach statistical significance between the GATTEX and placebo groups. It may be that QoL issues related to PN dependence may in fact not only be related to volume reduction but other parameters such as daily time spent to set up PN, time worrying about PN, planning the day around PN, and overall technology dependence on PN which all may have played a role in defining PN dependence and were not fully explored in the SBS-QoL. Trends suggesting a potential impact on the daily lives of SBS patients were observed. Nine of the 17 single items showed improvement

that would likely impact the daily burden of SBS patients in the GATTEX group (Table 21).

Table 21. Comparison Within and Between Treatment Groups for Change at Week 24 from Baseline of Single SBS-QoL Items – Study CL0600-020

Item	GATTEX				Placebo				p-value Between Groups
	Median Baseline	Median Wk 24	Δ	p-value	Median Baseline	Median Wk 24	Δ	p-value	
Diarrhea/stomal output	6.4	3.6	-1.4	0.001*	7.3	5.3	-0.7	0.001*	0.495
GI symptoms	4.9	3.9	-1.2	0.007*	4.1	3.3	0.0	0.83	0.116
Sleep	5.1	3.3	-0.9	0.003*	4.2	3.3	0.0	0.527	0.081
Leisure activities	5.0	3.3	-0.9	0.024*	4.6	4.3	0.0	0.972	0.123
Everyday activities	4.8	3.8	-0.9	0.007*	5.0	4.2	-0.3	0.157	0.499
Skeleton/muscle symptoms	4.4	3.6	-0.6	0.002*	3.8	3.6	-0.1	0.445	0.240
Social life	5.4	4.0	-0.5	0.018*	5.2	3.9	-0.1	0.469	0.301
Physical health	5.2	4.1	-0.4	0.021*	4.4	3.9	-0.4	0.325	0.354
Fatigue/ weakness	5.7	4.8	-0.3	0.033*	4.8	4.4	-0.4	0.647	0.210
Diet, eating, & drinking habits	4.1	3.0	-0.4	0.213	4.4	4.2	0.0	0.630	0.421
Emotional life	4.9	4.6	-0.4	0.154	4.2	4.5	-0.2	0.414	0.638
Working life/ability to work	6.0	5.9	-0.4	0.223	5.9	4.6	-0.2	0.132	0.943
Energy level	5.0	4.7	-0.9	0.051	4.8	4.5	0.1	0.476	0.455
General wellbeing	4.2	3.6	-0.2	0.052	4.6	3.5	-0.1	0.338	0.630
Mobility & self-care activities	3.2	2.9	-0.2	0.271	2.5	2.2	-0.1	0.528	0.613

Table 21. Comparison Within and Between Treatment Groups for Change at Week 24 from Baseline of Single SBS-QoL Items – Study CL0600-020 (Continued)

Item	GATTEX				Placebo				p-value Between Groups
	Median Baseline	Median Wk 24	Δ	p-value	Median Baseline	Median Wk 24	Δ	p-value	
Other symptoms/ discomfort	3.3	3.8	-0.2	0.511	4.0	3.8	0.1	0.657	0.791
Pain	3.1	3.8	0.0	0.920	2.2	2.9	0.0	0.546	0.737

7.4 Conclusions from Study CL0600-020

Based on the results of Study 020, GATTEX at a dose level of 0.05 mg/kg/day for up to 24 weeks of treatment was superior to placebo in reducing the volume of PN/IV in adult SBS subjects while maintaining nutritional status (Table 50).

8.0 Efficacy in Long-term Extension Studies

SBS is a chronic, debilitating disease with many patients requiring lifelong PN/IV therapy. Therefore, it is important to examine the long-term benefit of treatment benefit of GATTEX.

SBS patients participating in the placebo-controlled trials of GATTEX were offered an opportunity to enroll into 1 of 2 extension trials. Study 005 is a completed long-term extension study to Study 004 that enrolled subjects for an additional 28 weeks. Study 021 is an ongoing extension study to Study 020 in which GATTEX 0.05 mg/kg/day is being evaluated for up to 2 years; interim data from this study is providing continued evidence of sustained response. Importantly, more than 90% of the SBS subjects who completed their participation in a placebo-controlled trial of GATTEX elected to continue treatment in a long-term extension study.

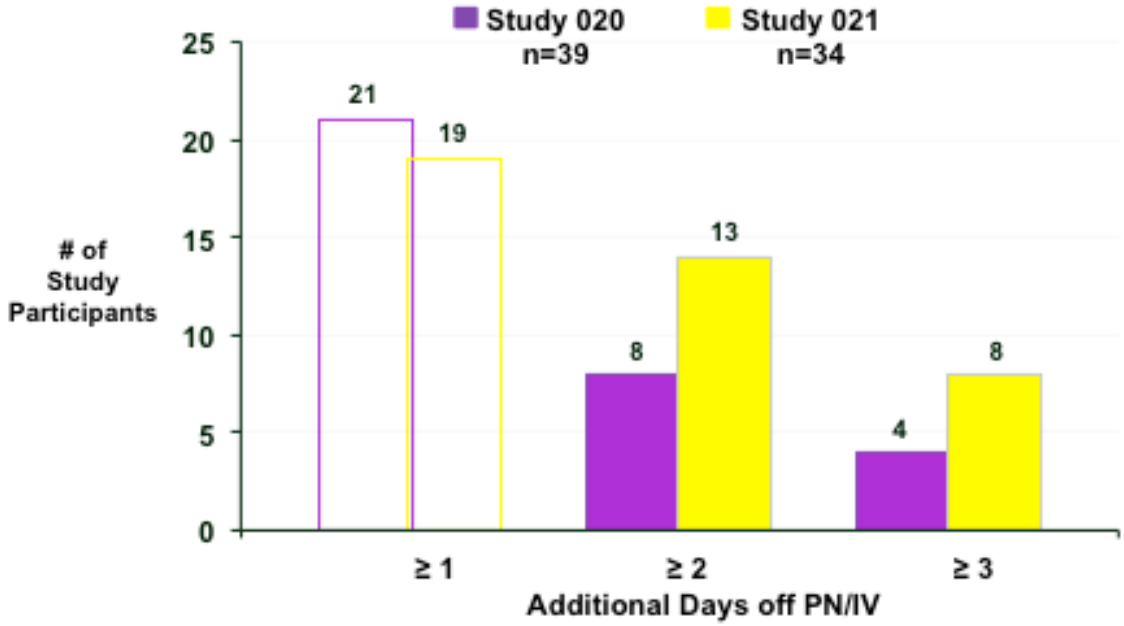
The study design and efficacy results for the long-term extension studies of GATTEX are presented in Appendix B. A summary of the findings for clinical responder rate, reduction in the number of days per week that PN/IV was required, and a description of the subjects able to completely wean of PN/IV with GATTEX 0.05 mg/kg/day in Study 021 follow.

Of 34 subjects in Study 021 who have been treated with GATTEX for at least 1 year (6 months in Study 020 and 6 months in Study 021), 31 (72% of the original 43 subjects treated in Study 020) were determined to be clinical responders at 1 year (i.e., ≥20% reduction from baseline), including all 25 GATTEX responders in Study 020 and 6 of 9 subjects who did not meet responder status at month 6 in Study 020.

Long-term treatment with GATTEX resulted in an additional reduction in the number of days per week that PN/IV was required. A reduction in PN/IV support of at least 2 days per week was achieved in 13 (of 34, 38%) subjects after treatment with GATTEX for 1 year (vs. 8 of 39 subjects, 21% after 6 months in Study 020) (Figure 20). A reduction in

PN/IV support of at least 3 days was achieved in 8 (of 34, 24%) subjects after treatment with GATTEX for 1 year (vs. 4 of 39 subjects, 10%, after 6 months in Study 020).

Figure 20. Additional Days Off PN/IV with 6 Months Additional Exposure to GATTEX in Long-term Extension Study 021



8.1 GATTEX Patients Who Permanently Discontinue PN/IV Treatment

Across the phase 3 studies, as of the April 11, 2012 amendment to the NDA, 10 of 134 subjects treated with GATTEX 0.05 mg/kg/day were weaned completely from PN/IV therapy. Subjects were weaned from PN/IV as early as 3 months and as late as 27 months after initiation of GATTEX (Table 22). With 8 of 10 patients being weaned after 6 months, the findings suggest that long-term use is associated with continued improvement. Specific information on subjects who have completely weaned can be found in Table 23.

In the phase 3 studies with GATTEX, subjects had an aerage of 6 years from their putative surgery leading to SBS and were therefore considered to have permanent dependence on PN/IV support. Spontaneous weaning in this population is a highly unanticipated outcome; therefore, 10 subjects treated with 0.05 mg/kg/day who were weaned from PN/IV therapy is strongly supportive of GATTEX efficacy as well as consistent with long-term improvement in intestinal function caused by GATTEX. For the 10 of 134 (7.5%) patients treated with GATTEX at 0.05 mg/kg/day who are now independent of PN/IV, this allows for the removal of the central line and elimination of the risks associated with central lines and parenteral nutrition including sepsis, liver disease, and thrombosis.

Table 22. Duration of GATTEX Treatment when Completely Weaned Off PN/IV Support

Duration of Treatment with GATTEX	Number of Patients
0 to < 3months	0
3 to < 6 months	2
6 to <12 months	3
12 up to 24 months	5

Table 23. Summary of SBS Subjects Who Permanently Discontinued PN/IV Treatment

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6 [a]	Subject 7	Subject 8	Subject 9	Subject 10
Original Study	004	004	004	020	020	020	020	020	020	020
GATTEX dose (mg/kg/day)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Age (years), gender	61, M	54, M	66, M	50, M	46, F	41, F	55, F	66, F	39, M	69, F
Reason for resection	Mesenteric infarction	Mesenteric venous infarction	Ischemic bowel	Ulcerative colitis	Crohn's disease	Injury	Micro-vascular of unknown process	Enteritis radio-therapy	Injury	Mesenteric arterial infarction
Colon in continuity	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Remaining small intestine (cm)	80	28	48	250	250	55	46	80	50	120
Duration of PN/IV dependency (years) at time of discontinuation	6.5	25	2	1.5	1.5	2	10	7	13	5.25
PN/IV requirement at baseline (L/week)	3.5	5.4	12	13	3.5	5.6	4.95	4.35	6.75	3.5
PN/IV requirement at baseline (days/week)	4	3	6	6	3	6	3	3	3	3
Duration of GATTEX treatment at the time of PN/IV wean-off (weeks)	12	16	52	32	28	78	87	89	75	101
Duration of independence from PN/IV at the time of data cut-off (weeks)	48[b]	41[b]	3[b]	84[b]	88[b]	12[b]	0[c]	14[c]	13[c]	0[c]

L=liters; PN/IV=parenteral nutrition/intravenous hydration

[a] Subject 6 received placebo in 020; [b] Completed study; [c] Data cutoff = 31 May 2012

9.0 Clinical Safety

9.1 Overview of GATTEX Safety Development Program

The safety database for the GATTEX Development Program includes data from 15 clinical studies: 9 clinical pharmacology studies; 4 phase 3 studies in adult subjects with SBS; and 2 exploratory studies in subjects with active Crohn's disease. As of 30 June 2011, all studies were complete with the exception of Study 021, a phase 3 two-year extension study in adult subjects with PN-dependent SBS. The data cutoff date for safety data presented in the Briefing Book is 31 October 2011, including data presented in the 4-Month Safety Update.

As shown in Table 24, a total of 566[1] subjects were treated with GATTEX and 198 subjects were treated with placebo. Of the 566 subjects treated with GATTEX, 299 subjects were treated in the Clinical Pharmacology Studies, 173 subjects were treated in SBS phase 3 studies, and 94 subjects were treated in Other Studies (active Crohn's disease). The 2 SBS placebo-controlled studies are the largest controlled studies ever conducted in subjects with SBS.

1 The total number of unique subjects treated with GATTEX was actually 565, as 1 subject who was treated with GATTEX in Study 92001 also received GATTEX in Study 004 and in extension Study 005.

Table 24. Number of Subjects by Study Group – Safety Population (All Studies)

Study Group	Placebo	GATTEX	Total Exposed
Clinical Pharmacology Studies	114	299	344
Single-dose Studies	77	188	196
Healthy	77	158	166
Hepatic Impaired	0	12	12
Renal Impaired	0	18	18
Multiple-dose Studies	37	111	148
Healthy	37	94	131
SBS	0	17	17
Phase 3 SBS Studies	59	173	180
Placebo-controlled	59	109	168
Uncontrolled	0	153 (89)	153 (141)
Other Studies (Active Crohn's disease)	25	94	100
Placebo-controlled	25	75	100
Uncontrolled	0	65 (46)	65 (65)
Grand Total Subjects	198	566[a]	624

n = number; SBS = short bowel syndrome

Note: The values in parentheses correspond to the count of subjects in the cell total who have already been counted in the same column and primary study group by virtue of having participated in the placebo-controlled study. Subjects who received both GATTEX and placebo in a crossover study are counted once in the Placebo column, once in the GATTEX column, and once in the Total column.

a. The total number of unique subjects treated with GATTEX was actually 565, as one subject who was treated with GATTEX in 2 separate studies.

Source: SCS, 4-Month Safety Update Table 2

The Clinical Pharmacology Studies were short-term, with study drug treatment ranging from 1 day (a single dose) to up to 3 weeks. The SBS phase 3 studies were long-term; the treatment period in SBS placebo-controlled studies was 24 weeks in duration, and the long-term extension Study 005 was 28 weeks in duration. The treatment duration of ongoing extension Study 021 is up to 2 years. The treatment period for an exploratory study in subjects with active Crohn's disease, Study CL0600-008 (hereafter referred to as Study 008), was 8 weeks and its extension, Study CL0600-009 (hereafter referred to as Study 009), was 12 weeks in duration.

For each of the phase 3 SBS studies, an external, independent Data Safety Monitoring Board (DSMB), comprised of physicians with relevant training and an independent statistician (not associated with the Sponsor, study centers, or investigators), reviewed data on a routine basis and could have had access to unblinded data for safety assessments, if necessary. The DSMB was restricted to individuals free of significant conflicts of interest. The DSMBs did not identify any safety issues during the phase 3 studies.

Table 35 (In Appendix C) summarizes the safety assessments presented in this Briefing Document, showing the visits (by study) at which AEs were monitored, clinical laboratory tests and ECGs were performed, and vital signs were measured.

9.2 Description of Safety Population

The ITT and safety populations were virtually identical; demographics and other baseline information for the ITT population are provided in Section 6.2 for Study 004, in Section 7.2 for Study 020.

9.3 Extent of Exposure

Exposure data for GATTEX and placebo, by study group and duration, across all studies are presented in Table 25.

GATTEX

Across all studies, 566 subjects were exposed to GATTEX, 368 (65.0%) for less than 3 months and 198 (35.0%) for 3 months or longer, with a maximum of 132 weeks (Table 25). Of the 566 GATTEX-treated subjects, 140 (24.7%) were exposed to GATTEX for at least 6 months and 97 subjects (17.1%) were exposed for at least 12 months. The mean duration of exposure to GATTEX was 17.4 weeks, and the total number of person-years of exposure was 189.8 years. Most subjects were exposed to GATTEX in the clinical pharmacology studies (299/566 subjects; 52.8%); however, the greatest duration of exposure to GATTEX, defined by person-years, occurred in the SBS phase 3 studies (163.2 person-years).

Placebo

Over all studies, 198 subjects (34.9%) were exposed to placebo, only 1 of whom was exposed for 6 months or longer, and none for 12 months or longer (Table 25). The mean duration of exposure to placebo was 8.2 weeks and the number of person-years was 31.1. The maximum exposure for placebo-treated subjects was 28 weeks. The greatest number of subjects exposed to placebo was in the Clinical Pharmacology Studies (114/198 ubjects, 57.6%), and the greatest duration of exposure, defined by person-years, occurred in the SBS phase 3 studies (26.2 person years).

Table 25. Exposure to Study Drug – Safety Population

Category	SBS Phase 3 Studies		All Studies	
	Placebo (N=59)	GATTEX (N=173)	Placebo (N=198)	GATTEX (N=566)[a]
Mean (SD)	23.069 (4.4584)	49.064 (25.6903)	8.155 (10.3391)	17.434 (25.8661)
Min / Max	2.86 / 28.00	0.57 / 132.0	0.14 / 28.00	0.14 / 132.0
<1 week n (%)	0	4 (2.3)	77 (38.9)	176 (31.1)
1-<4 weeks n (%)	1 (1.7)	6 (3.5)	39 (19.7)	153 (27.0)
4-<8 weeks n (%)	2 (3.4)	4 (2.3)	7 (3.5)	17 (3.0)
8-<12 weeks n (%)	0	3 (1.7)	19 (9.6)	14 (2.5)
12-<16 weeks n (%)	0	5 (2.9)	0	15 (2.7)
16-<20 weeks n (%)	1 (1.7)	0	1 (0.5)	5 (0.9)
20-<24 weeks n (%)	15 (25.4)	3 (1.7)	15 (7.6)	37 (6.5)
24-<36 weeks n (%)	40 (67.8)	25 (14.5)	40 (20.2)	26 (4.6)
36-<48 weeks n (%)	0	16 (9.2)	0	16 (2.8)
≥48 weeks n (%)	0	107 (61.8)	0	107 (18.9)
<3 months n (%)	3 (5.1)	18 (10.4)	142 (71.7)	368 (65.0)
3-<6 months n (%)	55 (93.2)	15 (8.7)	55 (27.8)	58 (10.2)
6-<12 months n (%)	1 (1.7)	43 (24.9)	1 (0.5)	43 (7.6)
≥12 months n (%)	0	97 (56.1)	0	97 (17.1)
Number of person years of exposure	26.18	163.23	31.05	189.76

Max=maximum; Min=minimum; N, n=number; SD=standard deviation; SBS=short bowel syndrome

Notes: Percentages for duration of exposure are based upon the number of subjects in the Safety Population. Percentages for duration of dose exposure are based upon the number of subjects in the Safety Population who obtained that dose. Duration of exposure is defined as: (last GATTEX dose date - first GATTEX dose date + 1) / 7. For duration of dose exposure, subjects in CL0600-009 and incorrectly rechallenged subjects in ALX-0600-92001 are displayed in the dose level the subject was administered at the time. Duration of exposure categories represent intervals and are not cumulative.

Note: Three month intervals are defined as 91 days, with the exception that 360 days is used as the definition for 12 months. Person-years of exposure is defined as the total weeks of exposure for all subjects divided by 52 weeks.

a. The total number of unique subjects treated with GATTEX was actually 565, as one subject who was treated with GATTEX in Study ALX-0600-92001 (Subject ID: 0003 0021) also received GATTEX in Study CL0600-004 and in extension Study CL0600-005 (Subject ID: 0130-0001).

Source: SCS, 4-Month Safety Update Table 4

GATTEX was administered SC in every study, and also IV in Study 006, a comparative bioavailability study.

Across the 14 completed studies, the GATTEX dose was either a fixed nominal dose or was based on body weight (mg/kg). Weight-based dosing was employed in 2 of the 9 Clinical Pharmacology Studies (Study 006 and Study 92001), in all 4 SBS Efficacy and Safety Studies, and in both of the exploratory studies of active Crohn's disease.

For reporting purposes, all nominal fixed doses were converted to weight-based doses. Administered doses were categorized into the following weight based dosing groups: <0.05 mg/kg/day, 0.05 mg/kg/day, > 0.05 to 0.10 mg/kg/day, >0.10 to 0.25 mg/kg/day, and >0.25 mg/kg/day.

Dose Regimens

Subjects were exposed to the greatest range of GATTEX doses in the Clinical Pharmacology Studies (<0.05 to >0.25 mg/kg/day). The greatest number of subjects exposed to 0.05 mg/kg/d (n=134) was in the SBS phase 3 studies. Subjects were counted once for each dosage regimen they received. Thus, the 565 unique subjects were exposed to 667 GATTEX treatment regimens. Across all study groups, 0.05 mg/kg/day was administered to 170 subjects: 118 (69.4%) were exposed for up to 6 months; 103 (60.6%) for up to 12 months; and, 75 (44.1%) for 12 months or longer (ISS, 4-Month Safety Update, Table 8.2.3).

Twelve subjects received less than and 485 subjects received more than 0.05 mg/kg/day (ISS, 4-Month Safety Update, Table 8.4.3): 219 received >0.05 to 0.10 mg/kg/d, 176 subjects received >0.10 to 0.25 mg/kg/d; and 90 subjects received >0.25 mg/kg/day. The maximum dose of GATTEX was 1.11 mg/kg/day, which was received by 2 of the 8 healthy subjects who received a nominal fixed dose of 80 mg per day for 8 consecutive days (Study 022).

9.3.1 All Phase 3 SBS Studies

The duration of exposure to GATTEX and to placebo across the phase 3 SBS studies (004, 005, 020, and 021) is summarized in Table 25.

A total of 173 subjects were exposed to GATTEX during the phase 3 SBS studies (134 treated with 0.05 mg/kg/d and 39 treated with 0.10 mg/kg/d), with an overall exposure to GATTEX of 163.2 person-years. Most subjects in the 0.05 mg/kg/day were exposed for at least 3 months (88.1%, 118/134), and approximately three-fourths (80.6%, 108/134) were exposed for 6 months or longer. Most subjects in the high-dose group were exposed for 3 months or longer (94.9%, 37 of 39 subjects) and the majority (82.1%, 32/39) were exposed for 6 months or longer.

Across the 4 studies, 81.0% of GATTEX subjects (140/173) were treated for at least 6 months, and 56.1% (97) were exposed for at least 12 months. The mean duration of exposure to GATTEX for all subjects was 49.1 weeks (0.05 mg/kg/d: 51.3 weeks and 0.10 mg/kg/day: 41.3 weeks) (ISS, 4-Month Safety Update, Table 9).

9.3.1.1 Phase 3, Placebo-Controlled SBS Studies

The duration of exposures to GATTEX and placebo in the SBS placebo-controlled Studies 004 and 020, individually and combined, is presented in Table 36 (Appendix C).

During the SBS placebo-controlled studies, 109 subjects were exposed to GATTEX (77 to 0.05 mg/kg/day and 32 to 0.10 mg/kg/day) for a total of 46.5 person-years. In these 2 studies, 59 subjects were exposed to placebo for a total of 26.2 person-years.

More subjects were exposed to GATTEX in Study 004 (67) than in Study 020 (42); however, the number of person-years of exposure to GATTEX 0.05 mg/kg/d was greater in Study 020 (18.4 years) than in Study 004 (13.9 years). The same was true for placebo (Study 020; n=43; 18.7 years; Study 004; n=16; 7.5 years).

9.3.1.2 Long-term Extension Studies of SBS

The duration of exposures to GATTEX in the SBS long-term extension Studies 005 and 021 is presented in Table 37 (in Appendix C). A total of 153 subjects were treated with GATTEX; 52 of those subjects had already been exposed for up to 24 weeks in Study 004 and 37 had been exposed for up to 24 weeks in Study 020. As of the cut-off date for the 4-Month Safety Update (31 October 2011), 119 subjects had been exposed to GATTEX 0.05 mg/kg/day and 34 subjects to GATTEX 0.10 mg/kg/day. The greatest exposure to GATTEX, 50.7 person-years, was in the GATTEX 0.05/0.05 mg/kg/day group.

9.4 Adverse Events

9.4.1 Methodology

NPS pooled all clinical data (from clinical pharmacology, SBS, and Crohn's disease studies) and reviewed a listing of all terms while blinded to treatment (placebo or active), duration of treatment, and subjects' disease status. All treatment-emergent AEs were included, which is especially appropriate given the Orphan Drug status of the product. This approach was intended to minimize any bias in considering terms. No consideration was given to the judgment of individual investigators or the sponsor's medical monitor to further avoid bias.

Once the list was generated by preferred terms (PT) and MedDRA System Organ Class (SOC) from all GATTEX studies, the PTs of all treatment-emergent AEs were medically reviewed and classified into AE groups (medical synonyms) that best communicated the same medical concept. No distinction was made regarding severity, causality, or seriousness of the AEs or frequency of AEs.

AEs that were reported under different PTs in the database that represented the same medical concept were pooled together as a single AE group to avoid diluting or obscuring a potential signal (e.g., asthenia, fatigue, and malaise were pooled into the AE group term of "asthenic conditions"). The AEs were grouped on a high MedDRA hierarchy level (i.e., high-level group term [HLGT] or high-level term [HLT]) to facilitate detection of general trends, which could have remained undetected if considered just on the preferred term level and scattered across SOCs. Moreover, PTs with multi-axial MedDRA hierarchy were reported in the AE group that best characterized the same medical concept. For example, increased laboratory values (blood glucose increased) and the AE of hyperglycemia were classified in one AE group.

The process for AE medical synonyms was not applied to displays for discontinuations due to AEs.

9.4.2 Overview of Treatment-Emergent Adverse Events

An overall summary of treatment-emergent AEs is presented in Table 38 (in Appendix C) for all 15 clinical studies and specifically within the combined phase 3 SBS studies (004, 020, 005, and 021) and in Table 26, in which the experience within the phase 3 placebo-controlled and long-term extension studies of SBS is shown.

In all studies, 74.9% (424/566) of GATTEX-treated subjects reported at least 1 treatment-emergent AE, with about two-thirds of subjects (68.4%, 387/566) reporting an event classified as mild in intensity. Fifty-eight subjects (10.2%) discontinued study drug prematurely due to a treatment-emergent AE. Treatment-emergent serious adverse events (SAEs) were reported in 21.0% (119/566) of GATTEX-treated subjects. Two GATTEX-treated subjects who experienced a treatment-emergent SAE had a fatal outcome (refer to Section 9.4.5 for details).

In the placebo-controlled SBS studies, 88.3% (68/77) and 96.9% (31/32) of subjects in the GATTEX 0.05 mg/kg/day and 0.10 mg/kg/day groups, respectively, reported at least 1 treatment-emergent AE, as compared to 83.1% (49/59) of placebo subjects. Treatment-emergent SAEs were reported in 36.4% (28/77), 34.4% (11/32), and 28.8% (17/59) of subjects in the respective treatment groups. Premature discontinuations due to an AE were numerically more common in the GATTEX 0.05 mg/kg/day group (10.4%, 8/77) than in the high-dose group (6.3%, 2/32) or placebo group (6.8%, 4/59), overall; and higher in the earlier study of the low-dose group than in the later study (Study 004 [17.1%, 6/35] vs. Study 020 [4.8%, 2/42]).

Table 26. Overall Summary of Treatment-Emergent Adverse Events in Phase 3 SBS Studies (Safety Population)

	SBS Placebo-Controlled Studies 020 and 004						Long-term Extension Studies 021 and 005							
	Placebo (N=59)		GATTEX 0.05 mg/kg/d (N=77)		GATTEX 0.10 mg/kg/d (N=32)		Placebo/0.05 mg/kg/d (N=57)		Placebo/0.10 mg/kg/d (N=7)		GATTEX 0.05/0.05 mg/kg/d (N=62)		GATTEX 0.10/0.10 mg/kg/d (N=27)	
Parameter	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**
Any treatment-emergent AE														
No	10	(16.9)	9	(11.7)	1	(3.1)	4	(7.0)	0		5	(8.1)	1	(3.7)
Yes	49	(83.1)	68	(88.3)	31	(96.9)	53	(93.0)	7	(100.0)	57	(91.9)	26	(96.3)
Treatment-emergent AE severity														
Mild	45	(76.3)	58	(75.3)	26	(81.3)	44	(77.2)	7	(100.0)	53	(85.5)	22	(81.5)
Moderate	34	(57.6)	50	(64.9)	24	(75.0)	43	(75.4)	4	(57.1)	43	(69.4)	15	(55.6)
Severe	16	(27.1)	25	(32.5)	6	(18.8)	24	(42.1)	2	(28.6)	18	(29.0)	8	(29.6)
Any treatment-emergent SAE	17	(28.8)	28	(36.4)	11	(34.4)	30	(52.6)	3	(42.9)	36	(58.1)	9	(33.3)

Table 26. Overall Summary of Treatment-Emergent Adverse Events in Phase 3 SBS Studies (Safety Population) (Continued)

	SBS Placebo-controlled Studies 020 and 004						Long-term Extension Studies 021 and 005							
	Placebo (N=59)		GATTEX 0.05 mg/kg/d (N=77)		GATTEX 0.10 mg/kg/d (N=32)		Placebo/0.05 mg/kg/d (N=57)		Placebo/0.10 mg/kg/d (N=7)		GATTEX 0.05/0.05 mg/kg/d (N=62)		GATTEX 0.10/0.10 mg/kg/d (N=27)	
Parameter	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**
Treatment-emergent SAE severity														
Mild	5	(8.5)	6	(7.8)	7	(21.9)	5	(8.8)	1	(14.3)	10	(16.1)	3	(11.1)
Moderate	7	(11.9)	16	(20.8)	2	(6.3)	18	(31.6)	3	(42.9)	17	(27.4)	2	(7.4)
Severe	8	(13.6)	12	(15.6)	4	(12.5)	16	(28.1)	1	(14.3)	16	(25.8)	4	(14.8)
Treatment-emergent AEs leading to premature discontinuation	4	(6.8)	8	(10.4)	2	(6.3)	10	(17.5)	1	(14.3)	5	(8.1)	4	(14.8)
AEs leading to death	0		0		0		2	(3.5)	0		0		0	

AE=adverse event; CRF= case report form, MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number; SAE=serious adverse event.

Notes: Treatment-emergent AEs are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence. Values for relationship reported on the CRFs as possibly-related or probably-related are considered related, and values of unlikely-related are considered not related. Treatment-emergent AEs that do not have a relationship reported on the CRFs are considered related. All adverse events were coded using MedDRA version 12.0.

Source: ISS, 4-Month Safety Update, Table 42

With regard to the 141 subjects in the SBS studies who were treated with GATTEX for ≥180 days, 94.3% (133) reported at least 1 treatment-emergent AE, with the majority (88.7%, 125/141) reporting an event classified as mild in intensity. Eleven subjects (7.8%) treated for ≥180 days discontinued study drug prematurely due to a treatment-emergent AE (Table 39 in Appendix C).

9.4.3 Commonly Reported Treatment-Emergent AEs

9.4.3.1 Phase 3, Placebo-Controlled SBS Studies

Table 27 summarizes treatment-emergent AEs that were reported for ≥5% of the 109 GATTEX-treated subjects in placebo-controlled SBS studies. The most commonly reported treatment-emergent AEs (>15%) with GATTEX were abdominal pain (38.5%), upper respiratory tract infection (27.5%), nausea (26.6%), injection site reactions (20.2%), abdominal distension (16.5%), headache (16.5%), catheter sepsis (15.6%), GI stoma complication (15.6%), and urinary tract infections (15.6%). The frequency with which GI-related AEs were reported with GATTEX in the placebo-controlled SBS studies is not unexpected, as they are common in people suffering from SBS, as evidenced by findings in the placebo group. Of note, diarrhea, which is a main complaint of SBS patients, was more commonly reported in placebo subjects (11.9% vs. 6.4% with GATTEX).

A clear dose-response was not observed across reported AEs. Injection site reaction was the only meaningful treatment-emergent AE that was reported at a notably higher frequency in the GATTEX 0.10 mg/kg/day (40.6%, 13/32) vs. GATTEX 0.05 mg/kg/day (11.7%, 9/77).

Table 27. Summary of Treatment-Emergent Adverse Events Reported for ≥5% of GATTEX-Treated Subjects in Decreasing Order of Frequency – Placebo-Controlled SBS Studies (Safety Population)

Preferred Term	Placebo (N=59) n (%)	GATTEX 0.05 mg/kg/day (N=77) n (%)	GATTEX 0.10 mg/kg/day (N=32) n (%)	All GATTEX (N=109) n (%)
Abdominal pain *	16 (27.1)	29 (37.7)	13 (40.6)	42 (38.5)
Upper respiratory tract infection *	8 (13.6)	20 (26.0)	10 (31.3)	30 (27.5)
Nausea *	12 (20.3)	19 (24.7)	10 (31.3)	29 (26.6)
Injection site reactions *	7 (11.9)	9 (11.7)	13 (40.6)	22 (20.2)
Abdominal distension	1 (1.7)	15 (19.5)	3 (9.4)	18 (16.5)
Headaches *	9 (15.3)	10 (13.0)	8 (25.0)	18 (16.5)
Catheter sepsis *	10 (16.9)	12 (15.6)	5 (15.6)	17 (15.6)
Gastrointestinal stoma complication	3 (5.1)	13 (16.9)	4 (12.5)	17 (15.6)
Urinary tract infections *	10 (16.9)	11 (14.3)	6 (18.8)	17 (15.6)
Vomiting	6 (10.2)	9 (11.7)	6 (18.8)	15 (13.8)
Asthenic conditions *	7 (11.9)	8 (10.4)	6 (18.8)	14 (12.8)
Fluid overload *	4 (6.8)	9 (11.7)	2 (6.3)	11 (10.1)
Febrile disorders *	7 (11.9)	7 (9.1)	3 (9.4)	10 (9.2)
Catheter site related reaction *	8 (13.6)	8 (10.4)	1 (3.1)	9 (8.3)
Flatulence	4 (6.8)	7 (9.1)	2 (6.3)	9 (8.3)
Hypersensitivity *	3 (5.1)	6 (7.8)	3 (9.4)	9 (8.3)
Appetite disorders *	2 (3.4)	5 (6.5)	3 (9.4)	8 (7.3)
Musculoskeletal pain *	6 (10.2)	4 (5.2)	4 (12.5)	8 (7.3)
Arthralgia	3 (5.1)	4 (5.2)	3 (9.4)	7 (6.4)
Diarrhoea *	7 (11.9)	4 (5.2)	3 (9.4)	7 (6.4)

Table 27. Summary of Treatment-Emergent Adverse Events Reported for ≥5% GATTEX-Treated Subjects in Decreasing Order of Frequency – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Preferred Term	Placebo (N=59) n (%)	GATTEX 0.05 mg/kg/day (N=77) n (%)	GATTEX 0.10 mg/kg/day (N=32) n (%)	All GATTEX (N=109) n (%)
Gastrointestinal stenosis and obstruction *	0	3 (3.9)	3 (9.4)	6 (5.5)
Lower respiratory tract infection *	3 (5.1)	4 (5.2)	2 (6.3)	6 (5.5)
Sleep disturbances *	0	4 (5.2)	2 (6.3)	6 (5.5)

Studies included: CL0600-020, CL0600-004.

MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number.

Notes: Percentages are based upon the number of subjects in the Safety Population. Treatment-emergent adverse events are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence of System Organ Class and Preferred Term. All adverse events were coded using MedDRA version 12.0.

* Shows special interest in Body System or Organ Class. The preferred terms in the AE groupings represent medically similar terms.

Source: ISS, 4-Month Safety Update, Table 62

Table 40 (in Appendix C) shows treatment-emergent AEs occurring among the 141 subjects treated with GATTEX for 180 days or longer in SBS studies. The frequency of certain treatment-emergent AEs among subjects treated with GATTEX for 180 days or longer (Table 40) shows the same pattern as the placebo-controlled trials, with catheter sepsis (24.8%; 35/141), headaches (22.0%; 31/141), asthenic conditions (18.4%; 26/141), and weight decreased (15.6%; 22/141) being the most common.

Table 41 (in Appendix C) shows time to onset of AE data for all GATTEX-treated subjects in SBS studies. While GI-related AEs are common, they occur early (within the initial months) during treatment and then dissipate.

The most commonly occurring treatment-emergent AEs within the first 4 weeks of GATTEX therapy (i.e., reported in ≥ 5% of subjects) were: abdominal pain (22.5%,

39/173); nausea (15.0%, 26/173); injection site reactions (14.5%, 25/173); GI stoma complication (11.6%, 20/173); abdominal distension (7.5%, 13/173); headaches (7.5%, 13/173); upper respiratory infection (6.9%, 12/173); and fluid overload (5.2%, 9/173). Based on the mechanism of action of GATTEX, GI adverse events and fluid overload were not unexpected.

9.4.3.2 All GATTEX Studies

Across all studies, the treatment-emergent AEs reported for ≥15% of GATTEX-treated subjects were abdominal pain (30.0%), injection site reactions (22.4%), nausea (18.2%), and headache (15.9%) (Table 42 in Appendix C). There were no cases of angioedema, acute hepatic injury, Stevens-Johnson Syndrome, agranulocytosis, rhabdomyolysis, idiopathic thrombocytopenic purpura, Torsade de Pointes, or intussusception. One subject suffered from acute renal failure deemed by the investigator to be caused by nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme (ACE) inhibitor use. Two subjects were reported from 1 site in Poland with lung cancer. One of them subsequently died. In addition, in another Polish site, 1 subject with a history of Hodgkin's lymphoma died from a disseminated metastatic GI adenocarcinoma of unknown origin (coded as hepatic tumor). The deaths are discussed in more detail in Section 9.4.5. Cancer cases are discussed in Section 9.8.1.

9.4.4 Treatment-Emergent AEs Leading to Discontinuation

9.4.4.1 Phase 3, Placebo-Controlled SBS Studies

In the combined placebo-controlled SBS studies, 9.2% (10/109) of GATTEX-treated subjects and 6.8% (4/59) of placebo-treated subjects experienced at least 1 treatment-emergent AE that led to premature discontinuation of study drug. The rate of premature discontinuation was higher in the low-dose group (10.4%, 8/77) than in the high-dose group (6.3%, 2/32) or the placebo group (6.8%, 4/59). There was no trend in type of AE leading to premature discontinuation, with abdominal distension and constipation (n=2 each) the only preferred terms reported by more than 1 subject (Table 28).

As compared to the earlier experience in Study 004 with GATTEX 0.05 mg/kg/day (6/35, 17.1%), fewer subjects in Study 020 discontinued prematurely due to a treatment-emergent AE (2/42, 4.8%).

Table 28. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug in Decreasing Frequency Based on All GATTEX – SBS Placebo-Controlled Studies (Safety Population)

	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects with a treatment-emergent AE leading to premature discontinuation	4	(6.8)	8	(10.4)	2	(6.3)	10	(9.2)
Abdominal distension	0		2	(2.6%)	0		2	(1.8%)
Constipation	0		2	(2.6%)	0		2	(1.8%)
Abdominal pain	0		1	(1.3%)	0		1	(0.9%)
Asthenia	0		1	(1.3%)	0		1	(0.9%)
Cardiac failure congestive	0		1	(1.3%)	0		1	(0.9%)
Catheter sepsis	1	(1.7%)	0		1	(3.1%)	1	(0.9%)
Coma	0		1	(1.3%)	0		1	(0.9%)
Drug level increased	0		1	(1.3%)	0		1	(0.9%)
Dysgeusia	0		1	(1.3%)	0		1	(0.9%)
Haemorrhoidal haemorrhage	0		1	(1.3%)	0		1	(0.9%)
Hypersomnia	0		1	(1.3%)	0		1	(0.9%)
Nausea	0		1	(1.3%)	0		1	(0.9%
Pancreatitis	0		0		1	(3.1%)	1	(0.9%)
Small intestinal obstruction	0		0		1	(3.1%)	1	(0.9%)
Vomiting	0		1	(1.3%)	0		1	(0.9%)
Faecal volume increased	1	(1.7%)	0		0		0	
Frequent bowel movements	1	(1.7%)	0		0		0	
Intestinal polyp	1	(1.7%)	0		0		0	
Liver and small intestine transplant	1	(1.7%)	0		0		0	

AE=adverse event; MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number.

Notes: Treatment-emergent AEs are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence of Preferred Term. All adverse events were coded using MedDRA version 12.0.

Source: ISS, 4-Month Safety Update, Table 56

9.4.4.2 All GATTEX Studies

Table 43 (in Appendix C) summarizes all treatment-emergent AEs leading to premature discontinuation of GATTEX in all studies. Treatment-emergent AEs that led to premature discontinuation were reported in 10.2% (58/566) of GATTEX-treated subjects. Abdominal pain was the most common AE leading to premature discontinuation (3.7%, 21/566), followed by abdominal distension (1.2%, 7/566), Crohn's disease (1.1, 6/566%), and nausea (1.1, 6/566%). All other events caused premature discontinuation in less than 1% of subjects.

9.4.5 Deaths

Two GATTEX-treated subjects died shortly after discontinuation of treatment in Study 021. Vignettes for these subjects are presented in Appendix D. In addition, 1 subject died during the Screening Period of Study 004, prior to randomization and receipt of study drug. The investigator attributed the subject's death to a massive upper GI tract hemorrhage.

9.4.6 SAEs

9.4.6.1 Phase 3, Placebo-Controlled SBS Studies

In the combined placebo-controlled SBS studies, at least 1 treatment-emergent SAE was reported for 35.8% (39/109) of subjects treated with GATTEX and 28.8% (17/59) of subjects treated with placebo. Table 29 presents the SAEs reported by 2 or more GATTEX-treated subjects, with infection the most common (i.e., catheter-related sepsis [13.8%, 15/109], lower respiratory tract infection [2.8%, 3/109], and urinary tract infection [2.8%, 3/109]).

Table 29. Summary of Treatment-Emergent Serious Adverse Events Reported in ≥2 Subjects in Decreasing Frequency Based on All GATTEX – SBS Placebo-Controlled Studies (Safety Population)

	Placebo (N=59)	GATTEX 0.05 mg/kg/day (N=77)	GATTEX 0.10 mg/kg/day (N=32)	All GATTEX (N=109)
Subjects with ≥1 treatment-emergent SAE	17 (28.8)	28 (36.4)	11 (34.4)	39 (35.8)
Catheter sepsis*	9 (15.3)	11 (14.3)	4 (12.5)	15 (13.8)
Gastrointestinal stenosis and obstruction*	0	3 (3.9)	2 (6.3)	5 (4.6)
Biliary tract disorder*	0	3 (3.9)	0	3 (2.8)
Lower respiratory tract infection*	1 (1.7)	2 (2.6)	1 (3.1)	3 (2.8)
Urinary tract infections*	1 (1.7)	3 (3.9)	0	3 (2.8)
Catheter site related reaction*	1 (1.7)	2 (2.6)	0	2 (1.8)
Cognition and attention disorders and disturbances*	0	2 (2.6)	0	2 (1.8)
Device dislocation	2 (3.4)	0	2 (6.3)	2 (1.8)
Febrile disorders*	0	2 (2.6)	0	2 (1.8)

Studies include 020 and 004.

AE=adverse event; MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number; SAE=serious adverse event.

Notes: Treatment-emergent AEs are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence of Preferred Term. All adverse events were coded using MedDRA version 12.0.

* Shows special interest in Body System or Organ Class. The preferred terms in the AE groupings represent medically similar terms.

Source: ISS, 4-Month Safety Update, Tables 41 and 48

9.4.6.2 All GATTEX Studies

Across the 15 clinical studies, 21.0% (119/566) of GATTEX-treated subjects reported at least 1 treatment-emergent SAE. The only treatment-emergent SAE reported in >2% of subjects was catheter sepsis (7.1%; 40/566) (Table 44 in Appendix C). The differences in the nature and frequency of treatment-emergent SAEs across studies are consistent with the populations studied in the GATTEX development program.

9.5 Clinical Laboratory Findings

9.5.1 Clinical Chemistry

Table 45 (in Appendix C) presents baseline and mean change from baseline at endpoint for measures of liver function in the placebo-controlled SBS studies. Mean decreases from baseline at endpoint were observed in alkaline phosphatase, ALT, AST, total bilirubin, and GGT (gamma glutamyl transpeptidase) among GATTEX-treated subjects.

Table 46 and Table 47 (in Appendix C) present baseline and mean change from baseline at endpoint for measures of renal function and all other clinical chemistry tests, respectively, in the placebo-controlled SBS studies.

Mean change from baseline at endpoint was generally small for BUN, creatinine, sodium, potassium, phosphorous, chloride, bicarbonate, calcium, and glucose in the all GATTEX group, with no clinically significant differences in the analytes between the all GATTEX and placebo groups. Albumin, as a surrogate marker of overall nutrition, was reported to be lower in placebo-treated subjects (-1.6 g/L) vs. GATTEX-treated subjects (-1.1 g/L). There was a trend for higher lipase values in the GATTEX- compared to placebo-treated subjects (+13.8 U/L vs. +1.2 U/L; respectively) at endpoint; no between-group differences were seen in changes of amylase (+0.7 IU/L vs. -3.4 IU/L in the respective treatment groups). The clinical significance of isolated increase in lipase is unclear. Higher C-reactive protein (CRP) values were found in the GATTEX-treated subjects (+1.61 g/m^3) vs. placebo-treated subjects (-1.08 g/m^3) at endpoint. And, in Study 020, a

higher proportion of GATTEX-treated subjects exhibited CRP elevations above the reference range than placebo subjects; however, these abnormal CRP values were episodic and generally returned to baseline levels at following visits while subjects continued GATTEX treatment. Given the baseline characteristics of the study population, the clinical significance of increased CRP is not clear.

9.5.2 Hematology

Table 48 (in Appendix C) presents baseline and mean change from baseline at endpoint for hematology indices in the placebo-controlled SBS studies. Platelet values increased more so in the all GATTEX group than in the placebo group (+17.8 10^9/L vs. +1.0 10^9/L; respectively) at endpoint. Changes in the remaining hematology analytes were small in both the active and placebo groups. The most common markedly abnormal analyte was low hematocrit (≤37 % [M]; ≤32 % [F]) observed in 25 of 59 (42%) subjects taking placebo, 24 of 74 (32%) subjects treated with GATTEX 0.05 mg/kg/day, and 8 of 31 (26%) subjects treated with GATTEX 0.10 mg/kg/day (ISS, 4-Month Safety Update, Table 10.9.2).

9.6 Vital Signs

Table 49 (in Appendix C) presents baseline and mean change from baseline at endpoint for vital signs in the placebo-controlled SBS studies. No consistent, clinically meaningful trends in changes in vital signs from baseline were noted. The incidence of post-baseline markedly abnormal changes from baseline in systolic blood pressure, diastolic blood pressure, heart rate, and temperature were comparable between placebo and GATTEX in the placebo-controlled SBS trials (≤5.1% and ≤4.7% for placebo and GATTEX, respectively) (ISS, 4-Month Safety Update, Table 11.3.2).

Table 50 (in Appendix C) presents baseline and mean change from baseline at endpoint for body weight and BMI in the placebo-controlled SBS studies. While there was a suggestion of a dose-related increase in body weight with GATTEX in the placebo-controlled SBS studies, the mean increase from baseline to endpoint in the high-dose group (0.10 mg/kg/day) was only 1.3 kg.

In the long-term extension studies, mean body weight was stable (+1.1 kg in the 0.05/0.05 mg/kg/day group and +0.5 kg in the 0.10/0.10 mg/kg/day group of Study 005 and -0.1 kg in Study 021 at 28 weeks).

9.7 Electrocardiogram Results

Electrocardiogram assessments consisted of an assessment of baseline and endpoint routine 12-lead ECGs across all 15 clinical studies, a dedicated Thorough QT Trial (Study C09-001), a retrospective, exploratory analysis of ECG data from multi-dose clinical pharmacology study CL0600-022, and centrally read ECG data from multi-dose clinical pharmacology study C10-003. Mean change from baseline to endpoint ECG findings in the placebo-controlled SBS studies and results from the Thorough QT study are presented here.

Overall, the majority of baseline and endpoint ECGs were evaluated as normal. Across all GATTEX studies, only 2 subjects, both in the GATTEX 0.05 mg/kg/d treatment group of Study 020, had endpoint ECGs that were categorized as abnormal and clinically significant (Table 51 in Appendix C). A brief vignette of each case is provided below.

Subject 020-0106-1003 was a 72-year-old female with SBS and a history of left atrial septal defect who was enrolled in the GATTEX 0.05 mg/kg/d group of Study 020. ECG tracings were "normal" at screening, Baseline, and Week 4. ECG tracings showed a finding of "right atrial enlargement" at Weeks 20 and 24. A diagnosis and AE report of right atrial dilatation was made at the end-of-study visit, and the investigator classified the event mild in severity and not related to GATTEX use; no treatment was given. The subject enrolled in long-term Study 021 and the event was ongoing at the time of data cutoff for the NDA.

Subject 020-0147-1001 was a 40-year-old female with SBS and a negative cardiac history who was enrolled in the GATTEX 0.05 mg/kg/d group of Study 020. The ECG at screening is read as "normal" with ventricular rate of 68 beats per minute and QTc of 465 ms (at the upper limit of normal). The Week 24 ECG showed "nonspecific ST abnormality" and "QT prolongation; the ventricular rate was 90 beats per minute and the QTc was 484 ms. This subject entered the study with a borderline prolonged QTc; the slightly longer QTc at endpoint may be an artifact of heart rate and correction formula. Review of the ECG tracings showed no significant differences in ST segment morphology between Screening and Week 24. This subject likely had no clinically significant ECG changes from Baseline to endpoint.

Study C09-001 was a phase 1, randomized, 4-period, placebo- and active-controlled, single dose, change-over study in which the effect of GATTEX on cardiac repolarization and conduction in healthy subjects (QT, corrected QT [QTc] interval) was evaluated. In each period of the study, the subjects received one of the following treatments: GATTEX 5 mg SC, GATTEX 20 mg SC, placebo for GATTEX SC, or moxifloxacin, 400 mg oral (positive control). On a mg/kg/day basis, subjects who received the 5 mg dose of GATTEX received 0.05 to 0.10 mg/kg/day, and subjects who received the 20 mg GATTEX dose received 0.18 to 0.39 mg/kg/day. ECGs were recorded in triplicate at pre-dose (within 60 minutes before dosing), and at 1, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours post-dose.

After administration of moxifloxacin, the placebo-corrected change from predose baseline QTcF was 11.2 ms at 1 hour postdose and 13.8 ms at 4 hours postdose, its peak value. The results were positive for QTcF (i.e., all CIs for all comparisons to placebo did not contain zero).

The effect of GATTEX on cardiac repolarization (QTcF interval) was comparable to placebo. Following administration of GATTEX 5 and 20 mg, the placebo-corrected change from predose baseline QTcF ranged from -1.3 ms (12 hours postdose) to 1.3 ms (24 hours postdose), and from -1.1 ms (12 hours postdose) to 2.8 ms (5 hours postdose), respectively. The upper bound of the 95% one-sided CI was 3 ms for the 5 mg dose and 4.5 ms for the 20 mg dose, both being below 10 ms for the largest mean effect.

9.8 Special Safety Topics

9.8.1 Neoplasms

In a carcinogenicity study in the Wistar Han IGS rat, sponsored by NPS, the survival of teduglutide-treated animals (both male and female) was comparable to that of the control groups. Statistically significant treatment-related neoplastic changes included benign tumors of the bile duct epithelium seen in male rats treated at 35 mg/kg/day (at an incidence of 5/50) and adenomas of the jejunal mucosa seen in 5/50 males treated at 35 mg/kg/day. The NOEL for benign neoplastic changes associated with treatment with teduglutide was considered to be 3 mg/kg/day, yielding a systemic exposure of 2.3 ng•hr/mL, which is 9.8-times the human exposure at the recommended dose of 0.05 mg/kg/day. No treatment-related malignant tumors were observed following treatment with teduglutide in this rat carcinogenicity study.

Preliminary results of the 2-year carcinogenicity study in Crl:CD1 (ICR) mice did not show a statistically significant change in survival in either sex.

Adenocarcinoma in the jejunum had a significant positive trend ($p = 0.0155$), although none of the treated groups had a significant increase in this case ($p = 0.1084$ at 12.5 mg/kg/day). The positive trend in jejunal adenocarcinoma was due to a

nonsignificant increase at 12.5 mg/kg/day in the males (Table 3). The 12.5 mg/kg/day dose resulted in an exposure level 150 (AUC) and 480 (C_{max}) times the recommended human dose of 0.05 mg/kg/day.

The absence of adenoma in the jejunum of males suggests no biological continuity between the mechanistically-induced hyperplasia (generally minimal at all dose levels) and the occurrence of adenocarcinoma. However, this is a rare tumor in Crl:CD1 (ICR) mice and therefore the occurrence in the high-dose males may be test article related.

The possibility of a tumor-promoting effect has been investigated in a well-known mouse model of colon carcinogenesis (Thulesen et al., 2004; Iakoubov et al., 2009). Although a synthetic Gly-GLP-2 (same or similar amino acid sequence as teduglutide, but different manufacturing process) was used, these studies are considered relevant to a carcinogenic risk assessment of GATTEX. Prolonged treatment with Gly-GLP-2 promoted (i.e., accelerated) growth of tissue that had already existing cancer or tissue that was exposed to known carcinogens in the mouse intestine. These findings are in contrast to other studies. Specifically a xenographic cancer transplant study conducted by Koehler *et al*. examined the effects of exogenous native GLP-2(1-34) on proliferation and survival of colon cancer cells in vitro and in human colon xenografts implanted in nude mice (Koehler et al, 2008). Chronic exogenous native GLP-2(1-34) administration did not significantly increase the weight, number, or growth of the intestinal tumor xenografts. In a study of 30 patients with colorectal adenocarcinoma and 20 patients with adenoma, biopsy samples of normal and diseased colon mucosa from each patient were examined for GLP-2R receptor expression. No patients with adenoma expressed GLP-2R, while 6 patients with colorectal adenocarcinoma expressed GLP-2R (Bengi et al, 2011).

Across the GATTEX development program 3 malignancies were reported. One subject, with a history of Hodgkin's disease had metastatic adenocarcinoma to the liver, probably of GI origin, and 2 subjects had lung neoplasms. Vignettes for these subjects are presented in Appendix D.

NPS has proposed a Risk Evaluation and Mitigation Strategy (REMS) program which will focus on communicating the product's potential risks to prescribers, including specifically the risk of acceleration of neoplastic growth and enhancement of colon polyp growth. The GATTEX risk management plan and REMS program is reviewed in Section 9.10.

9.8.2 Polyps

The GATTEX, all studies, treatment-emergent AE safety population database was searched for preferred terms related to GI polyps and associated conditions including benign and malignant tumors of the intestine and colon. The following terms were identified: "colonic polyp," "colorectal polyp", "duodenal polyp", "intestinal polyp," "gastrointestinal tract adenoma", and "rectal polyp".

GI polyp-related treatment-emergent AEs were reported for 7 subjects in the safety population of all GATTEX studies. None was malignant. Three cases occurred during the placebo-controlled SBS studies and 4 cases occurred during the long-term extension studies. In the placebo-controlled SBS studies, 1 placebo subject was diagnosed with polyps in the external peri-stomal area and 2 subjects treated with GATTEX 0.05 mg/kg/day were diagnosed with GI polyps. One subject, who had a colon polyp removed at baseline, was diagnosed with a hyperplastic polyp on treatment Day 155. The second subject was diagnosed with a colon polyp on Day 1 of GATTEX treatment (baseline colonoscopy) and was therefore not considered treatment emergent. The frequency of GI polyp related treatment-emergent AEs in placebo-controlled SBS trials was 0.9% (1/109) for GATTEX and 1.7% (1/59) for placebo.

In the long-term extension studies (Studies 005 and 021), four subjects were diagnosed with GI polyp-related treatment-emergent AEs. Two subjects had GI polyp-related treatment-emergent AEs in Study 005. Both subjects received placebo in Study 004 and were treated with GATTEX 0.10 mg/kg/day in Study 005. One subject was diagnosed with the AE "rectal polyp" reported on treatment day 189; histopathology revealed a hyperplastic polyp. The second subject, who had a colon polyp removed at baseline, was

diagnosed with the AE "rectal polyp" on treatment day 190; histopathology revealed a tubulovillous adenoma with low-grade dysplasia. In Study 021 two patients experienced GI polyps. One subject, who had a colon polyp removed at baseline, was diagnosed with a colorectal polyp on treatment day 230; histopathology report revealed 3 tubulovillous adenomas with low grade dysplasia and the second subject was diagnosed with a duodenal polyp on treatment day 87; a biopsy was not taken.

In Study 004, colon and small bowel biopsies were performed prior to GATTEX therapy and at study end. The biopsies were analyzed with regard to DNA, RNA, and protein as well as microscopically. No dysplastic changes occurred, and the DNA, RNA, and protein content were normal.

Colonic polyps are common in the western world. The prevalence of colonic polyps in Europe and North America is high, increases with age, and can be as high as 25% at age 50 years (Winawer et al, 1997). It is therefore not unexpected that GI polyp-related treatment-emergent AEs were reported during the GATTEX clinical program. To date, the treatment-emergent AE data in double-blind, placebo-controlled studies do not show a trend for the occurrence of GI polyps and related conditions in subjects with SBS treated with GATTEX for 24 weeks.

NPS has proposed a Risk Evaluation and Mitigation Strategy (REMS) program to assure communication to prescribers specifically about the risk of possible enhancement of colon polyp growth.

9.8.3 Biliary Disease

A thorough review of biliary tract-related AE data from the GATTEX all studies safety population was conducted. A total of 4 (3.7%) subjects treated with GATTEX and 1 (1.7%) with placebo were reported to have treatment-emergent biliary tract-related AEs in the placebo-controlled SBS trials. Of the 4 subjects, 3 subjects (of 77, 3.9%) were treated with GATTEX 0.05 mg/kg/day and 1 subject (of 32, 3.1%) was treated with GATTEX 0.10 mg/kg/day. All 4 of the GATTEX-treated subjects (but not the placebo

subject) were reported to have cholecystitis; two had a prior history of cholelithiasis and one had no corroboratory objective evidence of cholecystitis reported. One subject in the placebo group was reported with "GGT increased", which was preceded by an abnormally high GGT at Screening, therefore this subject was not counted. Two subjects required a cholecystectomy. No subject with biliary tract-related AEs discontinued prematurely from the placebo-controlled SBS studies due to such AEs.

Seven subjects in the phase 3 SBS extension studies (005 and 021) reported cholecystitis or cholelithiasis. Of the 7 subjects, 6 subjects were diagnosed with cholecystitis and 1 subject was diagnosed with cholelithiasis; 3 of the subjects had a history of cholecystitis or cholelithiasis at baseline. Two subjects had a cholecystectomy performed, of which one discontinued prematurely due to cholelithiasis.

In the placebo-controlled Crohn's disease study, one subject treated with GATTEX was reported with one episode of mild elevation of "blood alkaline phosphatase" and another GATTEX-treated subject was reported with "cholecystitis," but no objective evidence of this condition was documented. Moreover, the subject discontinued study participation early due to the concurrent AE of "Crohn's disease" exacerbation. "Cholangitis", which was not reported in the SBS and Crohn's disease double-blind studies, was reported in one subject in the Crohn's disease extension study (009). The subject also was reported to have cholecystitis; however, surgical pathology did not confirm this.

The frequency of GATTEX-treated subjects with treatment-emergent biliary tract-related categorical elevations in laboratory parameters in the SBS and Crohn's disease placebo-controlled trials was comparable to, or lower than, that for the placebo. No trends in the alkaline phosphatase, GGT, and total bilirubin treatment-emergent categorical changes were identified.

Although a higher number and frequency of subjects with cholecystitis was reported in GATTEX treatment groups in placebo-controlled SBS trials (4 cases [3.7%] vs. none in the placebo groups), all of the subjects enrolled in these studies had multiple risk factors for biliary tract disease; thus, the occurrence of biliary tract-related AEs is not unexpected

in the GATTEX-treated patient population. NPS has proposed a Risk Evaluation and Mitigation Strategy (REMS) program that through its communication plan will educate prescribers about the potential risk of biliary tract disorders.

9.8.4 Pancreatic Disease

Adverse events and laboratory data were reviewed for the GATTEX safety population to determine whether any trends in the occurrence of pancreatic disease or abnormalities could be identified. The GATTEX safety population database was searched for treatment-emergent AEs with pancreas-related preferred terms and the frequency of subjects with amylase or lipase elevations in GATTEX placebo-controlled trials was assessed.

Four subjects in placebo-controlled SBS studies with purported treatment-emergent pancreas-related AEs were found. Three of these subjects were treated with GATTEX and 1 with placebo. One GATTEX-treated subject with history of Crohn's disease and multiple abdominal surgeries was initially diagnosed with pancreatitis, however, a small bowel obstruction was documented by imaging; the obstruction was the likely cause of the concurrent elevated amylase and lipase values rather than pancreatitis.

The second GATTEX-treated subject with a history of chronic pancreatitis and elevations of alkaline phosphatase and amylase prior to GATTEX treatment was hospitalized with complications and manifestations of his underlying chronic pancreatitis. The subject recovered following ERCP stent placements and completed participation in Study 004 and extension Study 005.

The third GATTEX-treated subject with pancreas-related biochemical elevations reported as AEs, was not considered to be treatment emergent as the elevations occurred at various times prior to treatment. The placebo-treated subject who had amylase and lipase elevations reported as AEs had amylase elevations prior to treatment and had mildly elevated lipase; both amylase and lipase elevations could be related to this subject's underlying medical condition of Crohn’s.

In the SBS long-term extension studies, pancreas-related events were reported in 2 subjects. One subject enrolled in the SBS extension study 005 was diagnosed with the SAE "pancreatitis chronic" on treatment day 171. The diagnosis of chronic pancreatitis suggests a long-standing condition, characterized by episodic exacerbations. One subject in SBS extension Study 021 was diagnosed with acute pancreatitis on treatment day 445; this subject has a history of pancreatitis.

In placebo-controlled Crohn's disease Study 008, one subject had increased amylase and lipase values 29 days after the last of 3 doses of GATTEX, suggesting that study treatment was not the cause of the enzyme elevations. Another GATTEX-treated subject had mild elevations of amylase and lipase on 2 study visits; the subject was discontinued for noncompliance. A medical history of Crohn's disease may have been a contributory or causal factor in these cases of elevated amylase and lipase.

The other 4 subjects were enrolled in the Crohn's disease extension Study 009, and had AEs of "lipase increased" and/or "blood amylase increased". The rates of amylase and lipase elevations are generally high in patients with Crohn's disease. Therefore, asymptomatic and episodic elevations of these enzymes are not unexpected in clinical studies of subjects with Crohn's disease.

Patients with Crohn's disease are known to be at risk for episodic and asymptomatic elevations of serum amylase and lipase. In 1 cross-sectional study, hyperamylasemia and hyperlipasemia was found in 17% and 9% of Crohn's disease patients (Heikius et al, 1999). Moreover, the levels of both amylase and lipase were correlated with the extent of colonic disease and higher histologic activity. Similarly, another study found a 14% prevalence of asymptomatic amylase and lipase elevations in IBD patients (Bokemeyer 2002). It is believed that inflammatory bowel can release extra-pancreatic amylase and lipase, and increased intestinal absorption can raise blood levels of these enzymes.

Two subjects in clinical pharmacology Study 015, treated with GATTEX 10 mg, had isolated mild increases in lipase. The sensitivity and specificity of mild and isolated

elevations of lipase for pancreatitis is relatively low. The outlying lipase values in these subjects may have been spurious or of non-pancreatic origin.

The frequency of GATTEX-treated subjects with treatment-emergent amylase (32.1%) or lipase (24.8%) elevations in placebo-controlled SBS studies was comparable to, or lower than, that for placebo groups (42.4% and 27.1%, respectively). In the placebo-controlled Crohn's disease study, the incidence of amylase elevations was somewhat higher for the GATTEX group (14.7% vs. 4.0% for placebo) and lipase elevations were comparable between GATTEX and placebo groups (5.3% and 4.0%, respectively).

NPS has proposed a Risk Evaluation and Mitigation Strategy (REMS) program that through its communication plan will specifically educate prescribers about the potential risk of pancreatic disorders.

9.8.5 Liver Disease

Figure 21 through Figure 24 show the mean values by week for the pooled data from the SBS placebo controlled studies for ALT, GGT, AST and bilirubin, respectively. There was no evidence that GATTEX caused an increase of any analyte at any time point during study when compared to placebo.

Adverse events and laboratory data were reviewed for the GATTEX SBS and Crohn's disease safety population to determine whether any trends in the occurrence of liver disease or abnormality could be identified. Treatment-emergent AEs in the GATTEX SBS and Crohn's disease safety population database were searched for liver-related preferred terms and the frequency of subjects with elevations in liver-related laboratory measures in GATTEX placebo-controlled studies was analyzed and tabulated.

By way of background, liver disease (and eventual liver failure) is common among SBS patients being treated with IV/PN, more so than in many other patient types on parenteral nutrition (Cavicchi et al, 2000). Cavicchi and coworkers determined the prevalence of complicated liver disease among patients receiving home parenteral nutrition for permanent intestinal failure to be 26% at 2 years, 39% at 4 years, 50% at 6 years, and

53% at 8 years. In a related study, Chan and North American coworkers reported that approximately 1 in 5 intestinal failure patients who require home parenteral for more than 1 year develop chronic liver disease, with the incidence increasing over time (Chan et al, 1999). Liver disease is one of the main causes of death in patients with permanent intestinal failure.

Figure 21. Decreased ALT Levels throughout Study (SBS Placebo-Controlled Studies)

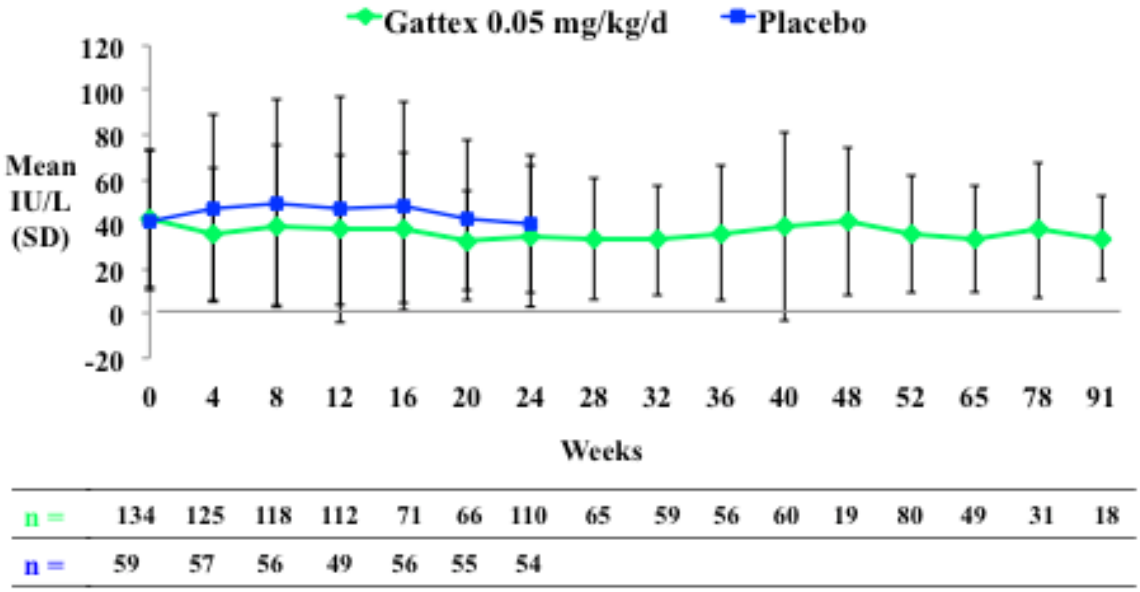


Figure 22. Decreased GGT Levels throughout Study (SBS Placebo-Controlled Studies)

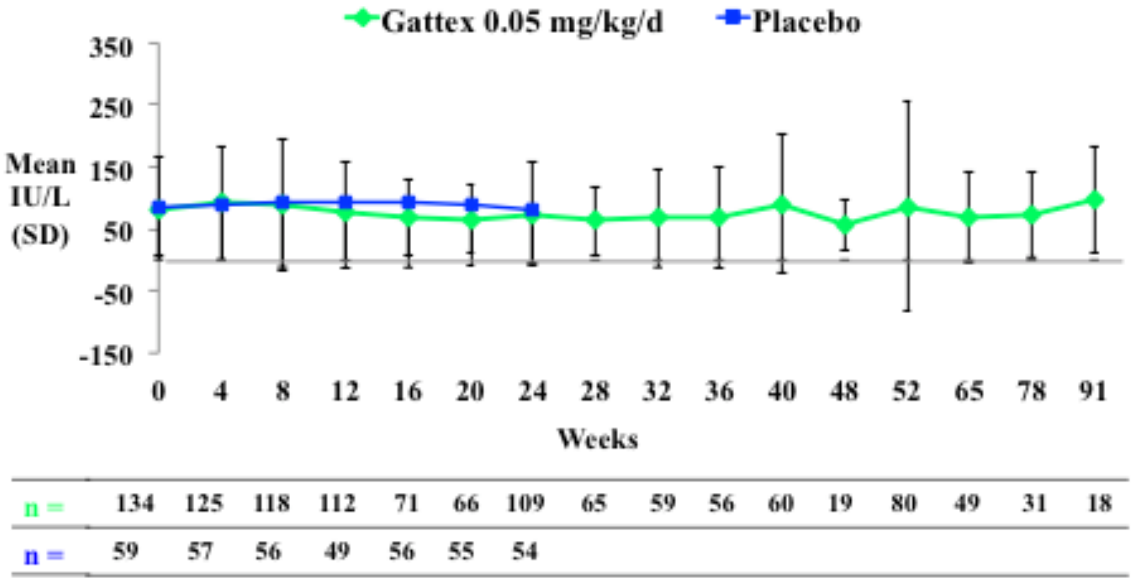
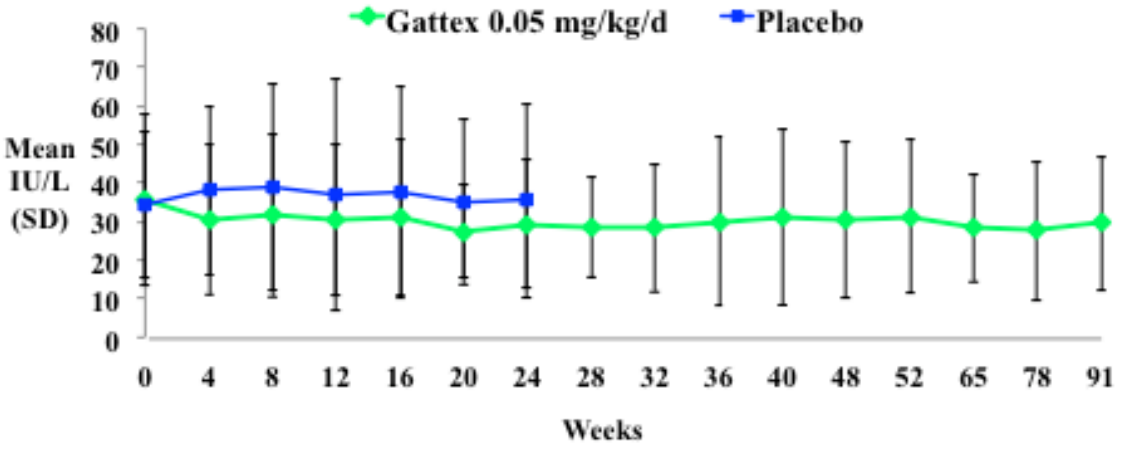
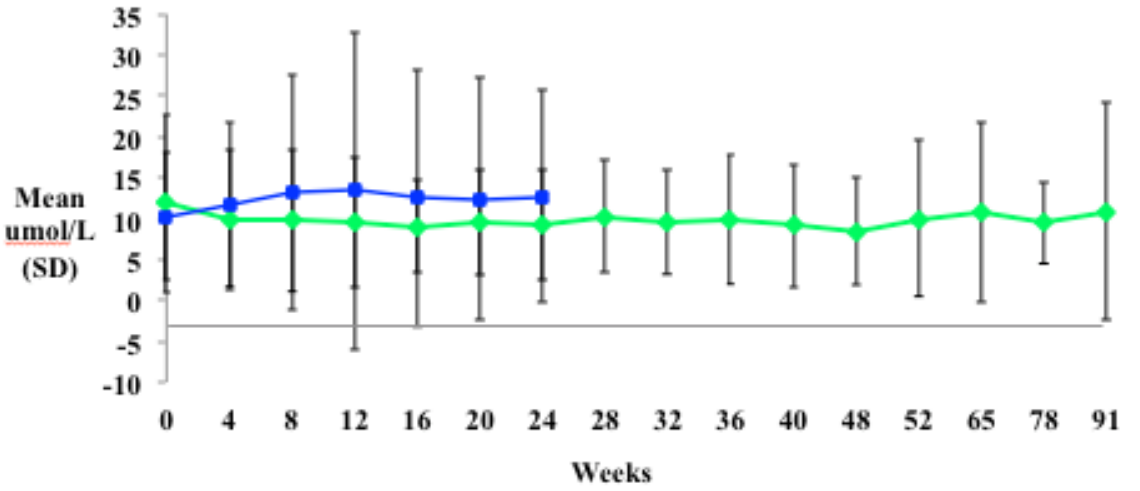


Figure 23. Decreased AST Levels throughout Study (SBS Placebo-Controlled Studies)



n =	134	123	118	112	71	66	110	65	59	55	60	18	80	49	31	18
n =	59	57	56	49	56	55	54									

Figure 24. Bilirubin Levels in SBS Placebo-Controlled Studies



n =	134	125	118	112	71	66	110	65	59	56	60	19	80	48	31	17
n =	59	57	56	49	56	55	54									

Treatment-Emergent Liver-Related AEs

In the SBS placebo-controlled studies, elevated liver function tests AEs were reported in 4 subjects treated with GATTEX (all of whom had pre-treatment elevations of their liver enzymes that worsened) and in 2 subjects with placebo. There were no Hy's law cases. Thus, the frequency of liver-related AEs in the placebo-controlled SBS studies was 3.7% (4/109) for GATTEX and 3.4% (2/59) for placebo. All subjects completed participation in their respective studies.

In the SBS extension studies, elevated liver function tests AEs were reported in 5 subjects that were not previously identified in the placebo-controlled studies. None of the cases met the Hy's Law criteria. Two subjects (005-0138-0010 and 021-0207-1001) had liver enzyme elevations deemed serious by the investigator. On Day 212 of GATTEX therapy, Subject 005-0138-0010, a 26 year-old female, was hospitalized for fever and was diagnosed with catheter sepsis. At the time of hospitalization liver enzymes were elevated: ALT 1000 IU/L (normal range 9-52), AST 850 IU/L (normal range 14-36) and were significantly improved at discharge: ALT 331 and AST 115.

Subject 021-0207-1001, a 23 year-old female, had elevated liver function tests on Day 178 of GATTEX therapy. The subject had a cholecystectomy and discontinued teduglutide use. Approximately two months after the cholecystectomy and 175 days after stopping GATTEX, the subject's transaminase levels began to increase. A liver ultrasound performed showed no abnormalities of the biliary tract. The investigator confirmed that the increase in liver enzymes could not be directly attributed to the study drug. The investigator further reported that the possible etiology of increased liver enzymes (i.e., an atypical post-surgical course of some abnormal response to PN) is not known. According to the subject's medical history, a mild increase in serum levels of these enzymes had also been observed before participation in the trial. The study drug was permanently discontinued.

In the SBS placebo-control studies, 1 subject (0203-1004) in the placebo group was diagnosed with the serious adverse event of hepatic cirrhosis on day 118 of the 020 study. The subject is a 49 year-old female, with a history cholestatic hepatitis and significant pre treatment elevations of ALT, AST and bilirubin prior to entering the 020 study. During the 020 study, a Fibroscan revealed a metavir liver fibrosis score of F4. Imaging studies obtained during the subject's hospitalization indicated severe and extensive fibrosis. This subject also experienced a worsening of ALT, AST and bilirubin while in the 020 study. The subject completed participation in Study CL0600-020.

In the SBS extension studies, 3 liver-related AEs were identified that were not previously identified in the placebo-controlled studies. One subject, a 46-year-old female, was diagnosed with a suspected hepatic cyst infection. CT and operative findings confirmed that the lesions were not intrahepatic. The second subject, an 82-year-old male, was diagnosed with worsening portal hypertension on treatment day 16 after the subject was hospitalized for abdominal pain and hematochezia. Gastroscopy revealed cholelithiasis and the diagnosis was acute biliary cholecystitis that was treated with antibiotics and biliary drainage; both events resolved. The third subject, a 50-year-old female, with a history of chronic cholestatic hepatitis, liver cirrhosis and Crohn's disease was diagnosed with portal hypertension on treatment Day 276. A liver Doppler ultrasound revealed chronic liver disease with signs of portal hypertension (patency of the paraumbilical vein) and as a result, the investigator temporarily discontinued GATTEX. Per the investigator, the portal hypertension was due to the progression of known liver disease related to intestinal failure and parenteral nutrition. GATTEX was discontinued due to multiple episodes of bleeding deemed due to mechanical trauma by the stoma bag.

In the double-blind Crohn's disease study, liver-related AEs were reported in 5 subjects (6.7%) treated with GATTEX; no cases were reported in placebo subjects. None of the cases were SAEs. Each of these subjects completed the study except for 1 subject who discontinued participation due to an unrelated AE. All of these subjects had mild, isolated elevations of ALT and/or AST. The numerical difference in frequency of liver-related AEs between the GATTEX and placebo groups was not confirmed by objective laboratory analyses, in which the frequency of GATTEX-treated subjects with treatment-emergent liver-related categories was similar to or lower than that for the placebo groups for both the SBS and Crohn's disease study populations, with no difference by dosing group.

In the Crohn's disease extension study, no new liver-related AE preferred terms or liver-related SAEs were reported.

Liver-Related Laboratory Abnormalities

The frequencies of pre-study treatment elevations of ALT, AST, and total bilirubin were approximately 35%, 29% and 7%, respectively, across all study subjects in the placebo-controlled SBS studies. For Study 004, inclusion criteria required that subjects had ALT and AST values <2 x ULN and total bilirubin values <1.25 x ULN. Study 020 excluded subjects with AST > 5 x ULN and total bilirubin > 2 x ULN. Thus, the high frequency of subjects with transaminase and bilirubin elevations observed at baseline is not unexpected.

Table 30 summarizes the frequencies of subjects in the placebo-controlled SBS studies with treatment-emergent elevations in specific liver-related categories. The categories are based on FDA guidance for drug-induced liver injury (Guidance For Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 2009). A 1.5-fold factor was added to the ALT and AST >3 x and >5 x categories, given that Study 004 included subjects with transaminase elevations up to 2 x and Study 020, up to 5 x the ULN. Overall, the frequencies of subjects with treatment-emergent elevated ALT, AST, and total bilirubin categories for GATTEX were similar to those for placebo (Table 30 on

next page). As discussed earlier (Section 9.5.1), mean decreases from baseline at endpoint were observed in alkaline phosphatase, ALT, AST, total bilirubin, and GGT among GATTEX-treated subjects (Table 45 in Appendix C).

Table 30. Frequency of Subjects With Treatment-Emergent Liver Related Categories in Placebo-Controlled SBS

Analyte	Placebo (N=59)	GATTEX 0.05 mg/kg/day (N=77)	GATTEX 0.10 mg/kg/day (N=32)	All GATTEX (N=109)
ALT				
>3 X ULN and > 1.5 X Baseline	1 (1.7%)	1 (1.3%)	2 (6.3%	3 (2.8%)
>5 X ULN and > 1.5 X Baseline	1 (1.7%)	1 (1.3%)	0	1 (0.9%)
>10 X ULN	0	0	0	0
>20 X ULN	0	0	0	0
AST				
>3 X ULN and > 1.5 X Baseline	0	1 (1.3%)	1 (3.1%)	2 (1.8%)
>5 X ULN and > 1.5 X Baseline	0	0	0	0
>10 X ULN	0	0	0	0
>20 X ULN	0	0	0	0
Total bilirubin				
>2 X ULN	2 (3.4%)	3 (3.9%)	1 (3.1%)	4 (3.7%)
>2 X ULN and ALT/AST >3 X ULN	0	0	0	0

Studies included: CL0600-004 and CL0600-020.
ALT=alanine aminotransferase, AST=aspartate aminotransferase, ULN=upper limit of normal
Source: ISS, 4-Month Safety Update, Table 110

9.8.6 Gastrointestinal Stenosis and Obstruction

Patients who have had multiple abdominal surgeries, such as those in the GATTEX clinical studies, are at higher risk for GI stenosis and obstruction (Barmparas et al, 2010; Hurst and Cohen, 2000). There were 12 unique subjects who reported a GI stenosis or obstruction related AE in the SBS studies. In the placebo-controlled SBS studies, incidence of GI stenosis or obstruction-related AEs was higher with GATTEX than with

placebo, with frequencies of 0% (0/59), 3.9% (3/77), and 9.4% (3/32) for the placebo, 0.05 mg/kg/day, and 0.10 mg/kg/day treatment groups, respectively. Of the 6 subjects who experienced GI stenosis or obstruction related AE, 3 subjects had a history of stenosis or obstruction and Crohn's Disease at baseline, 2 subjects had a history of stenosis or obstruction at baseline, and 1 subject had a history of Crohn's. In addition, 2/6 subjects required endoscopic dilatation; none of the events required surgical intervention.

In the long-term extension studies, 8 subjects experienced GI stenosis or obstruction related AE. Of the 8 subjects, 2 subjects had a recurrence of this AE from the placebo-controlled study. The 6 other subjects had a new onset treatment emergent AE. Two subjects had a history of stenosis or obstruction and Crohn's disease, 1 subject had a history of stenosis or obstruction at baseline, and 3 subjects had a negative history for both. One subject required endoscopic dilatation; none of the events required surgical intervention.

In the placebo-controlled Crohn's disease study, 1 subject (of 75, 1.3%) treated with GATTEX had a GI stenosis or obstruction-related AE. This subject underwent surgical intervention. Two additional cases were reported in the Crohn's disease extension study, 1 of which required surgical intervention.

In summary, all GI stenosis SBS cases resolved spontaneously, except for 3 subjects that required balloon dilation. It is possible that increased intestinal mass can exacerbate pre-existing intestinal stenoses and strictures.

NPS has proposed a Risk Evaluation and Mitigation Strategy (REMS) program that through its communication plan will educate prescribers about the potential risk of GI obstruction.

9.8.7 Respiratory Tract Infections

Bronchitis and lower respiratory tract infections were reported in the placebo-controlled SBS and Crohn's disease studies and in their respective extension studies. No such AEs were reported in the Clinical Pharmacology Studies.

In the SBS placebo-controlled studies, the frequencies of subjects with bronchitis and lower respiratory tract infections were similar in the GATTEX and placebo groups (5.2%, 6.3%, and 5.1% for GATTEX 0.05 mg/kg/day, 0.10 mg/kg/day, and placebo, respectively). SAEs were reported for 3 GATTEX-treated subjects and 1 placebo subject. However, no subjects discontinued study participation early because of a bronchitis or lower respiratory tract AEs.

In the placebo-controlled Crohn's disease study, there was only 1 AE of bronchitis (in a placebo subject) no AEs of lower respiratory tract infection. In the SBS and Crohn's disease extension studies, no preferred terms for bronchitis and lower respiratory tract infection were reported that had not been previously reported in Studies 004, 020, and 008.

Upper respiratory tract infection-related AEs occurred more frequently in GATTEX-treated subjects compared with those in the placebo groups in the placebo-controlled SBS studies (26.0%, 31.3%, and 13.6% for 0.05 mg/kg/day, 0.10 mg/kg/day, and placebo, respectively). None of the cases were reported as SAEs and no subject discontinued study participation prematurely as a result of an upper respiratory tract infection-related AE.

In the placebo-controlled SBS studies, the frequencies of selected medical history of Crohn's disease, splenectomy, asthma, and emphysema and concomitant corticosteroid use in subjects with upper respiratory tract-related AEs was not higher in the GATTEX groups as compared with the placebo group. Additionally, the durations of upper respiratory tract infection AEs were not longer for GATTEX versus placebo subjects. However, in the placebo-controlled Crohn's disease study, the occurrence of upper

respiratory tract infection-related AEs was similar for the GATTEX and placebo groups (10.7% and 12%, respectively). Although there were upper respiratory tract infection-related terms reported in the extension studies that had not been previously reported in Studies 004 and 008, these terms did not represent more serious or severe variants of upper respiratory tract infections.

In conclusion, upper respiratory tract infection-related AEs occurred in GATTEX-treated subjects at about twice the frequency of that in placebo group subjects in the placebo-controlled SBS studies but these AEs do not appear to be a cause of serious morbidity.

9.8.8 Immunogenicity

Teduglutide is manufactured in *E. coli* using recombinant technology. Because it is of a polypeptide nature, there is potential for formation of antibodies to GATTEX and to *E coli* protein (ECP). The potential for antibody development in subjects receiving GATTEX was evaluated in 7 clinical studies, 3 of which were long-term extension studies. Immunogenicity findings from these studies suggest the potential for the development of non-neutralizing antibodies to GATTEX, as well as antibodies to ECP. In general, subjects who develop antibodies respond to GATTEX treatment, further suggesting that the antibodies do not neutralize the drug product or have a significant effect on the pharmacokinetics of GATTEX. No subjects had evidence of systemic hypersensitivity or immune-related clinical symptoms. The presence of antibodies had no effect on pharmacokinetic parameters as determined for subjects in Study 004.

In Study 020, 6 subjects developed post-baseline antibodies to GATTEX that were non-neutralizing antibodies. One additional subject had a baseline sample low titer confirmed specific that was not run in the neutralizing antibody assay. These 7 subjects were all responders (a 20 to 100% PN/IV volume reduction at Weeks 20 and 24). There was no evidence of immune-related clinical pathologies in these subjects. The incidence of the anti-ECP antibody was greater in the GATTEX group compared to placebo group. There was no evidence of immune-mediated pathologies or hypersensitivity events in any

subjects who were teduglutide-specific antibody positive, cross-reactive to GLP-2, or neutralizing antibody-positive.

There is no evidence to suggest that anti-teduglutide antibody formation from long-term treatment affects the safety or efficacy of GATTEX. Twenty-seven of 85 subjects in extension Study 021 have developed anti-teduglutide antibodies as of the 4-month safety update. Three of these subjects experienced an injection site reaction, without any other hypersensitivity or immune-related clinical symptoms. Monitoring of all subjects who are GATTEX-antibody positive is ongoing in Study 021.

9.9 Safety Summary

The safety database for the GATTEX Development Program includes data from 15 clinical studies: 9 clinical pharmacology studies; 4 phase 3 studies in subjects with SBS; and 2 exploratory studies in subjects with active Crohn's disease. As of 31 October 2011, all studies were complete with the exception of Study 021, a phase 3 two-year extension study in adult subjects with PN-dependent SBS.

A total of 566 subjects were treated with GATTEX and 198 subjects were treated with placebo. Of the 566 subjects treated with GATTEX, 299 subjects were treated in the Clinical Pharmacology Studies, 173 subjects were treated in SBS phase 3 studies, and 94 subjects were treated in Other Studies (of Crohn's disease). Of the 566 GATTEX-treated subjects, 140 (24.7%) were exposed to GATTEX for at least 6 months and 97 subjects (17.1%) were exposed for at least 12 months. The 2 SBS placebo-controlled studies are the largest controlled studies ever conducted in subjects with SBS.

The most common treatment-emergent AEs with GATTEX (>15%) in the placebo-controlled SBS studies (and occurring at a frequency higher with GATTEX vs. placebo) were abdominal pain, upper respiratory tract infections, nausea, injection site reactions, abdominal distension, headaches, and gastrointestinal stoma complication. Injection site reactions occurred in 11.7% (9/77) of subjects with 0.05 mg/kg/day and 40.6% (13/32) of subjects with 0.10 mg/kg/day vs. 11.9% (7/59) of placebo subjects.

Across development 3 cases of cancer have been reported. A 48-year-old man with a history of Hodgkin's disease (diagnosed in 1988 and treated with chemotherapy and radiotherapy), cecal necrosis caused by radiation, and primary liver disease, was diagnosed with a metastatic adenocarcinoma 11 months after the start of treatment. A 64-year-old white male with a history of smoking (i.e., about 30 cigarettes/day for approximately 30 years) was diagnosed with non-small cell lung cancer after 87 days of GATTEX treatment. A 74-year-old male with a history of smoking 10 cigarettes a day for about 5 years and stopped approximately 25 years ago was diagnosed with lung squamous cell carcinoma stage unspecified.

Across development, GATTEX was well tolerated with low discontinuation rates (17% in the placebo-controlled SBS studies). The tolerability profile of GATTEX is mainly GI specific (consistent with the expected GI pharmacodynamic effects), and its safety profile supports both short-term and long-term treatment of SBS.

9.10 Risk Management Plan

The Risk Management Plan (RMP) for GATTEX serves as the basis for an action plan for pharmacovigilance and risk minimization activities. The RMP contains the safety specification which presents data on known and potential safety risks and areas of risk that have not yet been studied or not studied extensively; the Pharmacovigilance Plan which is an overview of planned pharmacovigilance activities; an SBS registry and the proposed REMS. The goals of the GATTEX REMS include:

- To utilize a communication plan to educate prescribers about the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction and pancreatic and biliary disorders.

An important part of risk mitigation is the full prescribing information, which is suggested to contain the following contraindication:

GATTEX is contraindicated in patients with active malignancy and in patients with a history of malignancies within the last five years (excluding basal cell carcinoma).

If any malignancy is diagnosed during GATTEX therapy, GATTEX must be discontinued.

The proposed REMS includes a communication plan that will educate prescribers about the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, GI obstruction and pancreatic and biliary adverse events. The communication plan will consist of a Dear Healthcare Provider Letter and a Dear Professional Society Letter.

In addition, patients will be enrolled in an SBS registry, which will include data collection: baseline demographics, etiology, colonoscopy (or alternate imaging) and laboratory results; ongoing laboratory, colonoscopy and other imaging studies, as well as PN/IV requirement. Post discontinuation of GATTEX, patients will be continued to be followed. The registry will be open to all SBS patients, but will focus on GATTEX- treated patients.

10.0 Benefit-Risk Conclusion

10.1 Unmet Medical Need

SBS is caused by a reduction in intestinal absorptive capacity that typically follows partial or complete surgical excision of the large or small intestine or occurs secondary to congenital intestinal abnormality or underlying intestinal disease. The extent of nutrition and fluid needs in SBS patients is dependent upon multiple factors including the amount of residual intestine and colon, presence of an ileal segment, and degree of spontaneous intestinal adaptation following resection. In the US, there may be up to 10,000 to 15,000 adult SBS patients requiring chronic PN/IV support (Oley Foundation for Home Parenteral Registry, 1992 and Enteral Nutrition and the American Society for Parenteral and Enteral Nutrition). Chronic PN/IV therapy is typically given 5-7 days a week for about 10 hours per day but is associated with significant increases in morbidity and mortality.

For SBS patients on chronic PN/IV therapy, the therapeutic goal is to decrease the need for PN/IV and ideally wean patients completely off PN/IV therapy, given the inherent PN/IV risks. Increasing the time off from PN/IV therapy can decrease the burden of illness suffered by SBS patients.

Optimal management of SBS may include a specialized oral diet, enteral feedings, parenteral nutrition, and fluid and micronutrient supplements. A specialized oral diet may consist of a high carbohydrate, low-fat diet, adjusted for individual patient requirements and preferences. Suboptimal treatment of SBS can ultimately lead to severe malnutrition, impaired cardiac, hepatic, and renal functions, fluid retention, intestinal mucosa atrophy, loss of intracellular minerals (zinc, magnesium, phosphorus), osteoporosis, diminished cell-mediated immune function, increased risk of infections, and eventually death. Thus, clinical care of SBS patients has focused on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, and anti-diarrheal and anti-secretory agents, using parenteral nutrition to supplement the patients' fluid and nutritional needs.

Intestinal transplant is the only treatment that potentially can restore absorptive capacity, but it is rarely performed because of the high associated morbidity and mortality. Often the main indications for intestinal transplant are recurrent central line infections, loss of vascular access, or complications of longstanding PN/IV support, such as progressive liver disease.

Thus, no current long-term treatment addresses the underlying issue of inadequate surface area and inadequate absorption of fluids and nutrients that is left in SBS patients and how best to optimize the remnant intestinal function. The ideal goal of intestinal rehabilitation is to increase intestinal absorption of orally ingested fluids and nutrients, allowing an opportunity for SBS patients to be completely weaned from long-term PN/IV therapy. A reduction in the volume of infusion or the number of hours per day necessary for chronic PN/IV therapy can lead to significant benefit in SBS patients.

Patient Perceptions of SBS

SBS is highly symptomatic condition with patients ranking diarrhea, dehydration, fatigue, nausea/abdominal cramping and diet limitation as the most frequent and bothersome symptoms (Acumen, July 2011). Patients with SBS want to eat but realize the consequences (Acumen, July 2011). Patients expressed a deep fear of diarrhea, which can occur up to 40 times per day (Acumen, July 2011), and public accidents which can leave them “confined” in their homes with the need to plan ahead and always be aware of bathroom locations (Acumen, Dec. 2010). Patients are socially and personally impaired, leading to feelings of isolation, social awkwardness and are sometimes linked to depression and overall “melancholy” (Acumen, Dec. 2010). The largest obstacle for SBS patients is the need to be “hooked-up” to PN for some 9-14 hours per day (TVG, Sept 2009).

Patient Perceptions of PN

The patients’ views of PN are mixed. They acknowledge that PN provides the nutrients they need to sustain life; however, they express resentment toward PN as being restrictive

and can result in a loss of independence (Acumen, Dec. 2010). Specifically, patients mentioned:

- PN impedes their ability to be spontaneous, travel, and interact socially (Acumen, Dec. 2010).
- Diet limitations and appliance complications (Acumen, July 2011).
- PN creates dependence. As a result, patients may feel limited, sick, and not normal (Acumen, Dec, 2010).
- PN affects sleep and impairs ability to work (Acumen, Dec. 2010).
- PN carries considerable risk of infection, which are traumatic experiences (Acumen, Dec. 2010). Infections are considered a "scary" issue for many patients, resulting in ER visits and prolonged hospitalization stays (over 1 week) (TVG, Sept. 2009; Acumen, July 2011).

10.2 Summary of Benefits

In Study 92001, GATTEX induced structural changes in the intestinal mucosa and increased absorption of important nutritional parameters (fat, nitrogen, sodium, potassium, calories, GI fluids), as measured based on fecal wet weight obtained through stool balance studies, with corresponding decreases in fecal and stomal loss of these key nutrients and calories. GATTEX increased absolute GI fluid absorption by almost 900 mL per day and decreased GI fluid losses (fecal or ostomy output) by approximately the same amount (-887 mL/24 hours) (each $p<0.001$ vs. baseline), representing approximately a 30% reduction in fecal losses in these SBS subjects that correlated with an increase in urine output of 508 mL/day ($p<0.001$ vs. baseline). Since intake was kept stable (no change in PN/IV volume and standardized diets), increased intestinal absorption was shown by not only a decrease in GI fluid losses, but also an increase in urine output.

In Study 004, there was supportive evidence that the 0.05 mg/kg/day group had a clinically meaningful reduction in PN/IV therapy and 2 patients completely weaned from PN/IV support. The nominal p value compared to placebo in the 0.05 mg/kg/day group was 0.007 for the primary endpoint. For the responder analysis (at least 20% reduction at both weeks 20 and 24, which is the primary endpoint in Study 020) in the 0.05 mg/kg/day group, the p value was 0.005. At Week 24, a mean weekly PN/IV volume reduction of -2.5 L was observed in both active treatment groups compared to -0.9 L for placebo (p=0.08 for each comparison of active versus placebo).

In addition, findings from intestinal biopsies in Study 004 affirmed the pharmacodynamic effect of GATTEX, as both GATTEX doses induced expansion of the absorptive epithelium by increasing villus height in the small intestine (GATTEX 0.05 mg/kg/day [p=0.0065] and GATTEX 0.10 mg/kg/day [p=0.0024]). Thus, while the preplanned statistical testing failed on the first dose tested, there was significant secondary evidence that GATTEX produced a clinically meaningful effect in the 0.05 mg/kg dose group.

In Study 020, the responder rate in the 0.05 mg/kg/day treatment group (27/43 subjects, 62.8%) was more than 2-fold greater than that observed in the placebo group (13/43 subjects, 30.2%). This difference was statistically significant (p=0.002). This PN/IV volume reduction translated into additional clinical benefit. Study 020 confirmed a strong intestinal absorptive effect leading to a decrease in PN/IV volume of 4.4 L/week after 24 weeks of treatment, with the potential of an additional 1 L/week after adjusting for the fluid composite effect. Weekly PN/IV support at Week 24 was reduced by 1 or more days in over half of subjects in the GATTEX group (53.8% [21/39 subjects]) vs. 23.1% (9/39) of placebo subjects (p=0.005). In order to more fully explore the magnitude of the additional days off PN/IV support, post hoc analyses were conducted looking at ≥2 and ≥3 or more additional days off per week. It was determined that 8 (of 39, 21%) GATTEX-treated subjects required ≥2 fewer days per week of PN/IV support, compared to 3 (of 39, 8%) placebo subjects. And, 4 (of 39, 10%) GATTEX-treated subjects required ≥3 fewer days per week of PN/IV support, compared to 2 (of 39, 5%) placebo subjects.

In the long-term extension trials, GATTEX 0.05 mg/kg/day is being evaluated for up to 2 years, thus providing evidence of sustained response. Of note, more than 90% of the SBS subjects who completed their participation in a placebo-controlled trial of GATTEX elected to continue treatment in a long-term extension study. Of 34 subjects in Study 021 who have been treated with GATTEX for at least 1 year (6 months in Study 020 and 6 months in Study 021), 31 (72% of the original 43 subjects treated in Study 020) were determined to be clinical responders at 1 year (i.e., ≥20% reduction from baseline) at 1 year, including all 25 GATTEX responders in Study 020 and 6 of 9 subjects who did not meet responder status at month 6 in Study 020.

Long-term treatment with GATTEX also resulted in an additional reduction in the number of days per week that PN/IV was required. A reduction in PN/IV support of at least 2 days per week was achieved in 13 (of 34, 38%) subjects after treatment with GATTEX for 1 year (vs. 8 of 39 subjects, 21% after 6 months in Study 020) A reduction in PN/IV support of at least 3 days was achieved in 8 (of 34, 24%) subjects after treatment with GATTEX for 1 year (vs. 4 of 39 subjects, 10%, after 6 months in Study 020).

Across the phase 3 studies 10 subjects treated with GATTEX 0.05 mg/kg/day were weaned completely from PN/IV therapy. Subjects were weaned from PN/IV as early as 3 months and as late as 27 months after initiation of GATTEX, suggesting long-term use is associated with continued improvement.

In summary, GATTEX has a significantly increases intestinal function and provides direct benefit to adult SBS patients. Specifically, GATTEX:

- increases intestinal surface area, as demonstrated on direct biopsy data
- increases nutrient absorption, as demonstrated on stool balance studies
- decreases GI fluid losses, as measured in strict inpatient setting

- increases fluid absorption, as measured by changes in intake and output on a standardized diet

These targeted effects in the intestine translate into clinical benefit as follows:

- GATTEX-treated subjects experienced, on average, a 40% reduction in PN/IV volume from baseline
- 54% of GATTEX-treated subjects experienced additional days off PN/IV support at 6 months
- PN/IV volume reductions and additional days off are sustained over time with GATTEX, with almost 25% of subjects now experiencing at least 3 additional days off per week of PN/IV at 1 year
- Ten patients on 0.05 mg/kg/day of GATTEX were completely weaned off their PN/IV.
- For GATTEX patients who are now independent of PN/IV, this allows for the removal of the central line and elimination of the risks associated with central lines and parenteral nutrition including sepsis, liver disease, and thrombosis.

10.3 Summary of Risks

In a nonclinical rat carcinogenicity study, statistically significant increases in benign tumors of the bile duct epithelium and adenomas of the jejunal mucosa were observed in male rats. No treatment-related malignant tumors were observed. The NOEL for the benign neoplasms was 9.8 times the human exposure at 0.05 mg/kg/day. Preliminary results in a mouse carcinogenicity study showed the presence of jejunal adenocarcinoma with minimal epithelial hyperplasia without adenoma. Jejunal adenocarcinoma is a rare tumor in Crl:CD1 (ICR) mice and therefore the occurrence in high-dose males (at 12.5 mg/kg/day) may be test article related. This dose represents an exposure level 150 (AUC) and 480 (C_{max}) times the recommended human dose of 0.05 mg/kg/day.

In the published literature, studies of a synthetic Gly-GLP-2 (with same amino acid sequence as GATTEX but different manufacturing process) found that prolonged treatment promoted (i.e., accelerated) growth of tissue that had already existing cancer or tissue that was exposed to known carcinogens in a mouse model of colon carcinogenesis (Thulesen et al, 2004; Iakoubov et al, 2009). NPS interprets these findings to mean that acceleration in the growth of neoplasms with GATTEX could not be ruled out and is proposing an SBS registry.

Across the development program, the safety profile of subjects in the GATTEX development program was consistent with the known characteristics of the SBS subject population, PN/IV infusions, or the pharmacologic effect of GATTEX. All of the potential risks of GATTEX use and limitations to its use, as outlined above, are considered acceptable and manageable in view of the high unmet need in the orphan disease of SBS with intestinal failure. The results from long-term extension studies of GATTEX demonstrate persistent and durable effects. Three cases of malignancy were reported. In all 3 cases, the subjects had known risks that were likely related to the development of cancer.

10.4 Conclusion

In summary, GATTEX treatment at a dose 0.05 mg/kg/day offers SBS patients the first long-term treatment that improves intestinal function and increases absorption of nutrients and fluids, allowing for reduction in PN/IV fluid support with the possibility of permanently terminating PN/IV therapy and its associated co-morbidities. The focused intestinal effects of GATTEX result in clinically meaningful improvements for SBS subjects and are the next step in their intestinal rehabilitation.

11.0 References

American Gastroenterological Association. American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124(4):1105-1110.

Barmparas G, Branco BC, Schnuriger B, Lam L, Inaba K, Demetriades D. The incidence and risk factors of post-laparotomy adhesive small bowel obstruction. J Gastrointest Surg. 2010;14(10):1619-1628.

Baxter JP, Fayers PM, McKinlay AW. A review of the quality of life of adult patients treated with long-term parenteral nutrition. Clin Nutr. 2006;25(4):543-553.

Bengı G, Kayahan H, Akarsu M, et al. Does glucagon like peptide-2 receptor expression have any effect on the development of human colorectal cancer? Turk J Gastroenterol. 2011;22(4):388-394.

Benjamin MA, McKay DM, Yang P-C, Cameron H, Perdue MH. Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. Gut. 2000;47:112-119.

Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the late effects study group. J Clin Oncol. 2003;21(23):4386-4394.

Birdwell SH, Hancock SL, Varghese A, et al. Gastrointestinal cancer after treatment of Hodgkin's disease. Int J Radat Oncol Biol Phys. 1997;37(1):67-73.

Bjerknes M, Cheng H. Modulation of specific intestinal epithelial progenitors by enteric neurons. Proc Natl Acad Sci USA 2001;98:12497-502.

Bokemeyer B. Asymptomatic elevation of serum lipase and amylase in conjunction with Crohn's disease and ulcerative colitis. Z Gastroenterol. 2002;40(1):5-10.

Boushey R, Yusta B, Drucker DJ. GLP-2 decreases mortality and reduces the severity of indomethacin-induced murine enteritis. Am J Physiol 1999;277:E937-47.

Boushey RP, Yusta B, Drucker DJ. Glucagon-like peptide (GLP)-2 reduces chemotherapy-associated mortality and enhances survival in cells expressing a transfected GLP-2 receptor. Cancer Res 2001;61:687-93.

Bremholm L, Hornum M, Henriksen BM, Holst JJ. Glucagon-like peptide-2 increases mesenteric blood flow in humans. Scand J Gastroenterol 2009;44:314-19.

Buchman AL. The clinical management of short bowel syndrome: steps to avoid parenteral nutrition. Nutrition 1997;13:907-13.

Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124:1111-34.

Cameron H, Yang P-C, Perdue MH. Glucagon-like peptide-2 –enhanced barrier function reduces pathophysiology in a model of food allergy. Am J Physiol. 2003;284:G905-G912.

Cameron HL, Perdue MH. Stress impairs murine intestinal barrier function: improvement by glucagon-like peptide-2. J Pharmacol Exp Ther. 2005;314:214-220.

Cavicchi M, Beau P, Crenn P, et al. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000;132(7):525-532.

Chan S, McCowen KC, Bistrian BC, Thibault A, Keane-Ellison M, Forse RA, et al. Incidence, prognosis, and etiology of end-stage liver disease in patients receiving home total parenteral nutrition. Surgery 1999;126:28-34.

Cheeseman CI, Tsang R. The effect of gastric inhibitory polypeptide and glucagon like peptides on intestinal hexose transport. Am J Physiol. 1996;271:G477-G482.

Cheeseman CI. Upregulation of SGLT-1 transport activity in rat jejunum induced by GLP-2 infusion in vivo. Am J Physiol. 1997;273:R1965-R1971.

Cottrell JJ, Stoll B, Buddington RK, Stephens JE, Cui L, Chang X, Burrin DG. Glucagon-like peptide-2 protects against TPN-induced intestinal hexose malabsorption in enterally refed piglets. Am J Physiol. 2006;290:G293-300.

Crenn P, Coudray-Lucas C, Thullier F, Cynober L, Messing B. Postabsorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. Gastroenterology. 2000;119:1498-1505.

Crenn P, Vahedi K, Lavergne-Slove A, Cynober L, Matuchansky C, Messing L. Plasma citrulline: a marker of enterocyte mass in villous atrophy-associated small bowel disease. Gastroenterology. 2003;124:1210-1219.

Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. Clin Nutr. 2008;27:328-329.

DaCambra MP, Yusta B, Sumner-Smith M, Crivici A, Drucker DJ, Brubaker PL. Structural determinants for activity of glucagon-like peptide-2. Biochem 2000;39:8888-8894.

De Boer AG, Wijker W, Bartelsman JF, De Haes HC. Inflammatory Bowel Disease Questionnaire: cross cultural adaptation and further validation. Eur J Gastro Hep. 1995;7:1043-1050.

DeLegge M, Absolaiman MM, Barbour E, Bassas S, Siddiqi MF, Moore NM. Short bowel syndrome: parenteral nutrition versus intestinal transplantation: Where are we today? Dig Dis Sci. 2007;52(4):876-892.

Drozdowski L and Thomson ABR. Intestinal hormones and growth factors: Effects on the small intestine. World J Gastroenterol 2009;15(4):385-406.

Drucker DJ, Ehrlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide-2. Proc Natl Acad Sci. USA 1996;93:7911-7916.

Drucker DJ, Yusta B, Boushey RP, DeForest L, Brubaker PL. Human [Gly2]GLP-2 reduces the severity of colonic injury in a murine model of experimental colitis. Am J Physiol 1999;276:G79-91.

Dubé PE, Brubaker PL. Frontiers in glucagon-like peptide-2: multiple actions, multiple mediators. Am J Physiol Endocrinol Metab 2007;293:E460-465.

Dudrick SJ, Latifi R and Fosnocht DE. Management of the short-bowel syndrome. Surg Clin North Am. 1991;71:625-643.

Estall JL, Drucker DJ. Glucagon-like peptide-2. Annu Rev Nutr. 2006;26:391-411.

EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy. 1990;16(3):199-208.

Fleiss JL, Levin B, Cho Paik M. Statistical Methods for Rates and Proportions, 3rd Edition. John Wiley & Sons Inc, New York; (2003):64-85.

Guan X, Stoll B, Lu X, Tappenden KA, Holst JJ, Hartmann B, Burrin D. GLP-2–mediated upregulation of intestinal blood flow and glucose uptake is nitric oxide–dependent in TPN-fed piglets. Gastroenterol. 2003;125:136-147.

Guan X, Karpen HE, Stephens J, Bukowski JT, Niu S, Zhang G et al. GLP-2 receptor localizes to enteric neurons and endocrine cells expressing vasoactive peptides and mediates increased blood flow. Gastroenterol 2006;130:150-164.

Hartmann B, Harr MB, Jeppesen PB, Wojdemann M, Deacon CF, Mortensen PB, Holst JJ. In vivo and in vitro degradation of glucagon-like peptide-2 in humans. J Clin Endocrinol Metab 2000;85:2884-2888.

Heikius B, Neimela S, Lehtola J, Karttunen T. Elevated pancreatic enzymes in inflammatory bowel disease are associated with extensive disease. Am J Gastroenterol. 1999;94(4);1062-1069.

Hollwarth ME. Short bowel syndrome: pathophysiological and clinical aspects. Pathophys. 1999;6:1-19.

Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2008. National Cancer Institute, Bethesda, MD. Available at: http://seer.cancer.gov/csr/1975_2008/. Based on November 2010 SEER data submission, posted to the SEER web site, 2011.

Hurst RD, Cohen RD. The role of laparoscopy and strictureplasty in the management of inflammatory bowel disease. Sem Gastrointest Dis. 2000;11:10-17.

Iakoubov R, Lauffer LM, Trivedi S, Kim YI, Brubaker PL. Carcinogenic effects of exogenous and endogenous glucagon-like peptide-2 in azoxymethane-treated mice. Endocrinology. 2009;150:4033-4043.

Jackson C, Buchman AL. Advances in the management of short bowel syndrome. Curr Gastroenterol Rep. 2005;7(5):373-378.

Jeppesen PB. Glucagon-like peptide-2: update on the recent clinical trials. Gastroenterology. 2006;130(Suppl 1):S127-S131.

Koch CG, Tangen CM, Jung J-W, Amara IA (1998). Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. Statistics in Medicine, Vol. 17, pp. 1863-1892.

Koehler JA, Harper W, Barnard M, Yusta B, Drucker DJ. Glucagon-like peptide-2 does not modify the growth or survival of murine or human intestinal tumor cells. Cancer Res. 2008;68(19):7897-7904.

Lloyd DA, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther. 2006;24(8):1231-1240.

Mardini HE, de Villiers WJS. Teduglutide in intestinal adaptation and repair: light at the end of the tunnel. Expert Opin. Investig. Drugs. 2008;17(6):945-951.

Meier JJ, Nauck MA, Pott A, Heinze K, Goetze O, Bulut K, Schmidt WE, Gallwitz B, Holst JJ. Glucagon-like peptide 2 stimulates glucagon secretion, enhances lipid absorption, and inhibits gastric acid secretion in humans. Gastroenterol. 2006;130:44-54.

Messing B, Crenn P, Beau P, Boutron-Ruault M, Rambaud J, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterol. 1999;117:1043-1050.

Munroe DG, Gupta AK, Kooshesh P, Vyas TB, Rizkalla G, Wang H, et al. Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide-2. Proc Natl Acad Sci USA 1999;96:1569-1573.

Nelson DW, Sharp JW, Brownfield MS, Raybould HE, Ney DM. Localization and activation of glucagon-like peptide-2 receptors on vagal afferents in the rat. Endocrinol. 2007;148:1954-1962.

Nightingale DJM. Management of patients with short bowel. Nutrition. 1999;15:633-637.

Nightingale J, Woodward JM. Guidelines for management of patients with a short bowel, Gut 2006;55:1-12.

Nørholk LM, Holst JJ, Jeppesen PB. Treatment of adult short bowel syndrome patients with teduglutide. Expert Opin Pharmacother. 2012;13(2):235-243.

Ng AK, Bernardo P, Weller E, et al. Second malignancy after Hodgkins disease treated with radiation therapy with or without chemotherapy: long-term risk and risk factors. Blood. 2002;100(6):1989-1996.

O'Keefe SJ, Buchman A, Fishbein T, Jeejeebhoy K, Jeppesen PB, Schaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol. 2006;4:6-10.

Orskov C, Hartmann B, Poulsen SS, Thulesen J, Hare KJ, Holst JJ. GLP-2 stimulates colonic growth via KGF, released by subepithelial myofibroblasts with GLP-2 receptors. Reg Peptides 2005;124:105-112.

Ramlau R, Didkowska J, Wojciechowska U, et al. Epidemiological situation concerning lung cancer in Wielkopolska in 1975-2002. Pneumonol Alergol Pol. 2006;74:179-185.

Rombeau JL, Rolandelli RH. Enteral and parenteral nutrition in patients with enteric fistulas and short bowel syndrome. Surg Clin North Am. 1987;67:551-571.

Scolapio JS, Fleming CR, Kelly DG, Wick DM, Zinsmeister AR. Survival of home parenteral nutrition-treated patients: 20 years of experience at the Mayo Clinic. Mayo Clin Proc. 1999;74(3):217-222.

Scott RB, Kirk D, MacNaughton WK, Medding JB. GLP-2 augments the adaptive response to massive intestinal resection in rat. Am J Physiol. 1998;38:G911-G921.

Shanbhogue LK, Molenaar JC. Short bowel syndrome: Metabolic and surgical management. Br J Surg. 1994;81:486-499.

Sigalet DL, Martin GR. Hormonal therapy for short bowel syndrome. J Pediatr Surg. 2000;35:360-364.

Sigalet DL, Wallace LE, Holst JJ, Martin GR, Kaji T, Tanaka H et al. Enteric neural pathways mediate the anti-inflammatory actions of glucagon-like peptide 2. Am J Physiol. 2007;293:G211-G221.

Stephens J, Stoll B, Cottrell J, Chang X, Helmrath M, Burrin DG. Glucagon-like peptide-2 acutely increases proximal small intestinal blood flow in TPN-fed neonatal piglets. Am J Physiol. 2006;290:R283-R289.

Stokes ME, Davis CS, Koch GG (1995). Categorical Data Analysis Using the SAS System., Cary, NC: SAS Institute Inc.

Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of secondary malignancy after Hodkgin's Disease in a collaborative cohort: the elation to age at treatment. J Clin Oncol. 2000;18(3):498-509.

Szczuka I, Roszkowski-Sliz K. Lung cancer in Poland in 1970-2004. Pneumonol Alergol Pol. 2008;76:19-28.

Tavakkolizadeh A, Shen R, Abraham P, et al Glucagon-like peptide 2: A new treatment for chemotherapy-induced enteritis. J Surg Res. 2000;91:77-82.

Tavares W, Drucker DJ, Brubaker PL. Enzymatic-and renal-dependent catabolism of the intestinotropic hormone glucagon-like peptide-2 in rats. Am J Physiol Endocrinol Metab. 2000;278(1):E134-E139.

Tazuke Y, Teitelbaum DH. Alteration of canalicular transporters in a mouse model of total parenteral nutrition. J Pediatr Gastroenterol Nutr. 2009;48(2):193-202.

Thulesen J, Hartmann B, Hare KJ, Kissow H, Ørskov C, Holst JJ, Poulsen SS. Glucagon-like peptide 2 (GLP-2) accelerates the growth of colonic neoplasms in mice. Gut. 2004;53:1145-1150.

Tsai CH, Hill M, Asa SL, Brubaker PL, Drucker DJ. Intestinal growth-promoting properties of glucagon-like peptide-2 in mice. Am J Physiol 1997;273:E77-E84.

Vanderhoof J and Langnas AN. Short-bowel syndrome in children and adults. Gastroenterol. 1997;113:1767-1778.

Vantini I, Benini L, Bonfante F, Talamini G, Sembenini C, Chiarioni G, Maragnolli O, Benini F, Capra F. Survival rate and prognostic factors in patients with intestinal failure. Dig Liver Dis. 2004;36(1):46-55.

Van Gossum A, Vahedi K, Abdel M, Staun M, Pertkiewica J. Clinical social and rehabilitation status of long term home parenteral nutrition patients, results of a European multicenter survey. Clincial Nurtrition. 2001;20(3):205-210.

Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). Medical Care. 1992;30:473-483.

Wilmore W, Byrne TA, Persinger RL. Short bowel syndrome: New therapeutic approaches. Curr Probl Surg. 1997;34:389-444.

Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112(2):594-642.

Winkler MF, Hagan E, Wetle T, Smith C, Maillet JO, Touger-Decker R. An exploration of quality of life and the experience of living with home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2010;34(4):395-407.

Wojdemann M, Wettergren A, Hartmann B, Holst JJ. Glucagon-like peptide-2 inhibits centrally induced antral motility in pigs. Scand J Gastroenterol. 1998;33:828-832.

Wojdemann M, Wettergren A, Hartmann B, Hilsted L, Holst JJ. Inhibition of sham feeding-stimulated human gastric acid secretion by glucagon-like peptide-2. J Clin Endocrinol Metab. 1999;84:2513-2517.

Xiao Q, Boushey RP, Drucker DJ, Brubaker PL. Secretion of the intestinotrophic hormone glucagon-like peptide 2 is differentially regulated by nutrients in humans. Gastroenterology. 1999;117:99-105.

Yusta B, Huang L, Munroe D, Wolff G, Fantaske R, Sharma S, et al. Enteroendocrine localization of GLP-2 receptor expression in humans and rodents. Gastroenterol. 2000;119:744-755.

Appendix A. Additional Efficacy Tables

Sensitivity Analyses – Study 020

The following sensitivity analyses were conducted to assess the impact of missing data, based upon cases where a scheduled visit after Week 2 was either not conducted, the weekly PN/IV volume could not be calculated for the preceding 14 days, or there was at least one of the preceding 14 days where a PN/IV value was not provided in the diary. Statistical testing was not conducted for the sensitivity analyses. All sensitivity analyses were based on a 20% to 100% reduction from baseline PN/IV volume at a visit and at the next scheduled visit.

Only subjects with a Week 24 dosing visit (completed the study)

Only subjects who completed the study (had a Week 24 dosing visit) were included in this sensitivity analysis. The subjects included in the analysis were treated in the same manner as in the primary efficacy analysis.

Obtain at least nine data points for Week 20 and/or Week 24

For cases where subjects had fewer than 9 non-missing PN/IV volumes recorded among the 14 days to be used for the primary analysis, data between Week 16 to Week 20 and Week 20 to Week 24 were explored to locate the last 9 days with non-missing values since the previous visit; all other subjects were treated in the same manner as in the primary efficacy analysis. The subject was considered a non-responder if there were fewer than 9 non-missing days available that were not excluded from the analysis due to a modification of PN/IV related to an AE.

Subjects excluded if interval PN/IV volume considered missing at Week 20 and/or Week 24 (Observed Case Analysis)

For cases where subjects had fewer than 9 non-missing PN volumes recorded among the 14 days at either of the two visit intervals to be used for the primary analysis, the subject

was excluded from the analysis. All other subjects were treated in the same manner as in the primary efficacy analysis.

Subjects as a non-responder if less than 14 days of PN/IV volume at Week 20 and Week 24 (Worst Case Analysis)

Subjects who had at least one day missing among the 14 days to be used at either Week 20 or Week 24 were considered a non-responder for this analysis. All other subjects were treated in the same manner as in the primary efficacy analysis.

Subjects excluded if less than 14 days of PN/IV volume at Week 20 and Week 24

Subjects who had at least one day missing among the 14 days to be used at either Week 20 or Week 24 were excluded for this analysis. All other subjects were treated in the same manner as in the primary efficacy endpoint.

Subjects as non-responders if PN/IV volume calculated as missing at any dosing visit after Week 2

Subjects for whom a PN/IV volume was classified as missing for the interval at any scheduled dosing visit between Week 4 and Week 24, inclusive, were considered a non-responder for this analysis. All other subjects were treated in the same manner as in the primary efficacy endpoint.

Subjects excluded if PN/IV volume calculated as missing at any dosing visit after Week 2 (complete case analysis)

Subjects for whom a PN/IV volume was classified as missing for the interval at any scheduled dosing visit between Week 4 and the end of the study was excluded for this analysis. All other subjects were treated in the same manner as in the primary efficacy endpoint.

Last two dosing visits used in place of Week 20 and Week 24

The demonstration of a 20% to100% reduction was examined based upon the last two consecutive visit intervals for which a response could be calculated, as opposed to being based on Weeks 20 and 24 regardless of whether a response could be calculated at both visits. Subjects had to have at a minimum both a Week 4 visit and a later dosing visit; early termination visits could be included as the second visit only if it took place at least 14 days after the previous dosing visit. Subjects with no set of visits that matched the criteria specified were considered a non-response for this analysis.

Table 31. Sensitivity Analyses of the Primary Efficacy Endpoint – Study 020 (Intent-to-Treat Population)

Response Status	Placebo (N=43)	GATTEX 0.05 mg/kg/day (N=43)
Completed the study, n (%)		
Number of subjects	39	39
Non-responder	26 (66.7)	12 (30.8)
Responder	13 (33.3)	27 (69.2)
Nine data points available since previous visit		
Number of subjects	43	43
Non-responder	30 (69.8)	16 (37.2)
Responder	13 (30.2)	27 (62.8)
Subjects excluded if response cannot be calculated at either visit		
Number of subjects	39	38
Non-responder	26 (66.7)	11 (28.9)
Responder	13 (33.3)	27 (71.1)
Subjects considered non-responders if missing PN/IV volume at any of the 14 days prior to visit		
Number of subjects	43	43
Non-responder	30 (69.8)	16 (37.2)
Responder	13 (30.2)	27 (62.8)
Subjects excluded if missing PN/IV volume at any of the 14 days prior to visit		
Number of subjects	37	38
Non-responder	24 (64.9)	11 (28.9)
Responder	13 (35.1)	27 (71.1)
Subjects considered non-responders if PN/IV volume missing for any dosing visit interval		
Number of subjects	43	43
Non-responder	30 (69.8)	17 (39.5)
Responder	13 (30.2)	26 (60.5)

Table 31. Sensitivity Analyses of the Primary Efficacy Endpoint – Study 020 (Intent-to-Treat Population) (Continued)

Response Status	Placebo (N=43)	GATTEX 0.05 mg/kg/day (N=43)
Subjects excluded if PN/IV volume missing for any dosing visit interval		
Number of subjects	37	36
Non-responder	24 (64.9)	10 (27.8)
Responder	13 (35.1)	26 (72.2)
Responder status of subjects with a 20% to 100% reduction based on the last two consecutive visit intervals		
Number of subjects	43	43
Non-responder	28 (65.1)	15 (34.9)
Responder	15 (34.9)	28 (65.1)

PN/IV=parenteral nutrition/intravenous.

Source: CSR Study 020, Tables 14.2.4.1, 14.2.4.2, 14.2.4.3, 14.2.4.4, 14.2.4.5, 14.2.4.6, 14.2.4.7 and 14.2.4.8

Appendix B. Long-term Extension Studies

STUDY 005

Study Design

Study CL0600-005 was a 28-week, randomized, double-blind, uncontrolled, parallel group, multicenter, multi-international extension study for with PN/IV-dependent SBS subjects who completed the 24-week Study 004. Subjects who received GATTEX in Study 004 received the same dose of GATTEX in the extension Study 005. Those who received GATTEX 0.05 mg/kg/day or GATTEX 0.10 mg/kg/day in both studies are referred to as the 0.05/0.05 or 0.10/0.10 treatment groups, respectively (otherwise known as the "1-Year Active Group"). Subjects who received placebo in Study 004 and GATTEX 0.05 mg/kg/day or GATTEX 0.10 mg/kg/day in Study 005 are referred to as the placebo/0.05 or placebo/0.10 treatment groups, respectively (otherwise known as the "6-Month Active Group"). GATTEX was administered by the SC route once daily into 1 of the 4 quadrants of the abdomen or either thigh.

To avoid unblinding Study 004, subjects received their blinded GATTEX dose group assignment at the time of randomization for Study 004, and the blinded assignments were maintained throughout Study 005. PN/IV support use was assessed at visits every 4 to 6 weeks throughout the study. For evaluation of efficacy data, the data at baseline of Study 004 served as baseline for the 1-Year Active Group and the data at the end of Study 004 (Week 24) served as baseline for the 6-Month Active Group.

Efficacy Endpoints

The efficacy endpoints in Study 005 were:

- Percentage of subjects who were responders in Study 004 (defined as at least a 20% reduction in Weekly PN/IV volume compared with Baseline of Study 004 at Week 20 and Week 24) and maintained or improved on that PN/IV fluid volume reduction at the end of Week 28 of Study 005

- Percentage of subjects who had a reduction of at least 20% compared with baseline in Weekly PN/IV volume at Week 28 (responders in Study 005)
- Volume of PN/IV fluid reduction at Week 28 compared to Baseline
- Number and percentage of subjects who discontinued PN/IV fluid
- Number and percentage of subjects who experienced reduced IV catheter access compared with Baseline at Week 28
- Absolute reduction from Baseline in PN/IV kilojoules at Week 28
- Absolute reduction from Baseline in weekly volume of PN/IV fluid at Week 28
- Changes from Baseline in plasma citrulline at Week 28
- Quality of life as measured by SF-36

Statistical Methods

Descriptive statistics were used to summarize the efficacy variables for each treatment group and overall. Response rates were compared among treatment groups using Pearson Chi-square test statistics. Continuous variables were compared among treatment groups using one-way analysis of variance with no adjustments for covariates or any baseline categorical variables. Paired t-tests were used to assess the significance of the change from baseline within treatment groups. Analyses and tabulations for all efficacy and safety data were based on the ITT population.

Disposition and Demographic and Other Baseline Characteristics

Of the 71 subjects who successfully completed Study 004, 65 subjects (91.5%) elected to enroll in Study 005. There were 25 subjects on GATTEX 0.05 mg/kg/day and 27 subjects on GATTEX 0.10 mg/kg/day from Study 004 who remained on the same GATTEX dose in Study 005. Of the 13 placebo subjects from Study 004 who entered

Study 005, 6 and 7 were randomized to GATTEX 0.05 mg/kg/day and 0.10 mg/kg/day, respectively. Of the 65 subjects enrolled in Study 005, 54 subjects completed and 11 subjects discontinued from the study.

The demographics and other baseline characteristics for subjects in Study 005 were similar to the results from Study 004, as expected given that all the subjects in Study 005 had participated in Study 004. Among the for subjects in the 1-Year Active Group, PN/IV volume at study entry was higher for those receiving GATTEX 0.10 mg/kg/day (13.1 L/wk) compared with subjects receiving GATTEX 0.05 mg/kg/day (9.8 L/wk). A similar difference was observed for subjects in the 6-Month Active Group (11.1 L/wk in GATTEX 0.10 mg/kg/day, 9.0 L/wk in GATTEX 0.05 mg/kg/day).

Efficacy Findings in Study 005

A brief summary of the key efficacy results from Study 005 is provided below.

- In the 1-Year Active Group, 75% of the subjects who were responders in Study 004 and entered Study 005 maintained a 20% to 100% reduction from baseline in PN/IV volume in both the GATTEX 0.05 mg/kg/day group (12/16 subjects) and the GATTEX 0.10 mg/kg/day group (6/8 subjects). The subjects who did not maintain response were excluded from the responder group, per the SAP, rather than being treatment failures (i.e., loss of diary confirmation of dose, lost to follow-up, hospitalization due to infection, and withdrawal due to AE).

- The number of included subjects who achieved a 20% to 100% reduction in PN/IV volume at Week 28 in the 1-Year Active Group in the GATTEX 0.05 mg/kg/day group was 68% (17/25), and in the GATTEX 0.10 mg/kg/day group 51.9% (14/27). Corresponding numbers for those who completed the 28 weeks with data were 89.5% (17/19) and 60.9% (14/23).

- In the 6-Month Active Group, 83.3% (5/6) of subjects in the GATTEX 0.05 mg/kg/day group and 42.9% (3/7) of subjects in the GATTEX

0.10 mg/kg/day group achieved a 20% to 100% reduction from baseline in PN/IV volume at Week 28.

- One subject in a 1-Year Active Group (0.05 mg/kg/day) completely discontinued PN/IV fluids after 52 weeks of treatment. In addition, the 3 subjects (2 and 1 in the 0.05 mg/kg/day and 0.1 mg/kg/day groups, respectively) who had weaned off PN/IV in Study 004 did not require PN/IV fluids during participation in Study 005, bringing the total to 4 GATTEX-treated subjects (vs. none in the placebo group) who were weaned off of PN/IV fluids at the completion of the long-term study.

- In the 1-Year Active Group, 68% (17/25) and 37% (10/27) of subjects in the low-dose and high-dose groups, respectively, achieved at least a 1-day reduction in PN/IV fluid use.

- In the 1-Year Active Group, 48% (12/25) of subjects treated with GATTEX 0.05 mg/kg/day experienced reduced need for IV catheter access. The corresponding result for the high-dose group was 37% (10/27 subjects).

- In the 1-Year Active Group, subjects on 0.05 mg/kg/day had a PN energy intake reduction of -14690 KJ/week and subjects on 0.10 mg/kg/day had a reduction of -6512 KJ/week after 52 weeks of treatment. In the 6-Month Active Group, the corresponding values were -5796 and -3209 KJ/week for the two groups, respectively, after 28 weeks of treatment.

- In the 1-Year Active Group, the mean reduction of PN/IV volume from Baseline to Week 28 was -4.9 L/week (57%) and -3.3 L/week (27%) in the 0.05 and 0.10 mg/kg/day groups, respectively. In the 6-Month Active Group, the corresponding results were -2.8 (34%) and -2.0 (26%) L/week.

- Plasma citrulline increased by 67.8% and 86.4% in subjects treated with 0.05 and 0.10 mg/kg/day, respectively, in the 1-Year Active Group. The corresponding increases in the 6-Month Active Group were 63.6% and 49.7%.

Conclusions from Long-term Extension Study 005

The results of Study 005 confirmed and supported those obtained in Study 004. The subjects who crossed over from placebo to GATTEX had a similar response rate as was seen in the placebo-controlled study; in addition, 4 subjects had completely weaned off PN/IV at the end of Study 005. The higher dose (0.10 mg/kg/day) did not provide any benefits over the lower dose (0.05 mg/kg/day).

STUDY 021

Study Design

Study 021 is an ongoing, long-term, open-label, multinational, multicenter study designed to monitor safety and PN/IV volume requirements at 2 weeks after the first dose of GATTEX, at monthly intervals for the first 3 months, and at 3-month intervals thereafter for PN/IV-dependent SBS subjects taking GATTEX. Of note, the visit schedule in Study 021 is not the same as it was in Studies 020 or 005. The lack of visits at months 4 and 5 may have affected the opportunity to further wean PN/IV, and therefore PN/IV volume decreases in subjects who received placebo in 020 and treatment-naïve patients enrolling directly into 021.

Subjects enrolled in this study completed 24 weeks of dosing in Study 020, or successfully completed Stage I (optimization/stabilization) in Study 020 (i.e., qualification for randomization), but were not treated because the target number of subjects (86) was already randomized. All subjects are to receive GATTEX 0.05 mg/kg/day, administered SC into 1 of 4 quadrants of the abdomen or either thigh or arm, regardless of their treatment group in Study 020. For subjects who successfully completed Stage I in Study 020 but were not randomized, the individual dose to be administered was a fixed dose of 0.05 mg/kg/day.

Duration of treatment in Study 021 is to be for a period of up to 2 years. Subjects may have had a maximum of 60 days off-treatment during the study (including between Studies 020 and 021). The data summarized below are based only on completed visits and events that occurred prior to the data cutoff date of 30 June 2011.

Efficacy Endpoints

The interim efficacy endpoints in Study 021 were:

- Absolute change and percent change from baseline in weekly PN/IV volume by visit

- Binary response status by visit, where response at a given visit was defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume, with additional binary response status variables based on 50% reduction, 75% reduction, and 100% reduction from baseline in weekly PN/IV volume
- Number of subjects who were weaned from PN/IV, and the time of stopping PN/IV support
- Change in days of weekly PN/IV volume
- Categorical reduction in days of weekly PN/IV volume
- Binary response status by visit based on prescribed weekly PN/IV volume
- Change from baseline in fluid composite effect
- Change from baseline in plasma citrulline

Statistical Methods

Descriptive summary statistics were used to summarize the absolute values and change from baseline (Study 020) at each time point for each treatment group for the actual PN/IV volume (L/week). Baseline was calculated from the first dose of active study drug received in Study 020 for subjects who received GATTEX in that study. Subjects who started active treatment in Study 021 (i.e., the 020 not treated/placebo group) had their last visit assessment from Study 020 as the new baseline for calculation purposes. No statistical tests for inferential purposes were performed in the interim analysis.

Disposition and Demographic and Other Baseline Characteristics

Of the 86 subjects who were randomized in Study 020, 78 completed the study and were eligible to participate in Study 021. Two subjects declined participation. Although Study 020 participants who stopped dosing prematurely due to non-drug related AEs were allowed to enter Study 021, no such subjects were actually enrolled. Twelve subjects, screened but not randomized (and hence, not treated) in Study 020 due to the closure of randomization, were eligible based on the inclusion criteria and entered Study 021 directly, bringing the total participants to 88. The 12 subjects screened but not randomized and the 39 subjects treated with placebo in Study 020 were designated the not-treated, placebo/teduglutide ("NT, PBO/TED") group, and the 37 subjects treated with GATTEX in Study 021 were designated the teduglutide/teduglutide ("TED/TED") group.

The majority of subjects were Caucasian (84/88 subjects, 95.5%), with 17.0% (15/88) ≥65 years of age. The gender distribution was 46.6% (41/88) male and 53.4% female (47/88). The demographic characteristics were comparable in the Study 020 teduglutide and Study 020 not-treated/placebo groups.

PN/IV history at screening was comparable between the treatment groups. The mean (±SD) years since start of PN/IV dependency was 6.41 (±6.27) years. Mean (±SD) prescribed weekly PN/IV volume at study entry was 13.74 L (±7.30). Mean prescribed days/week requiring PN/IV infusion was 5.9 (±1.59) days. Most of the subjects (89.8%) had a subclavian central venous IV access. The mean (±SD) prescribed weekly PN/IV volume at baseline was 12.07 L (±7.56). Mean prescribed days/week requiring PN/IV support was 5.6 (±1.68) days.

Efficacy Findings in Study 021

There were 2 subject populations in the ongoing Study 021:

- The TED/TED group represents those subjects already exposed to active treatment with GATTEX for 24 weeks in Study 020. All observations reported for the TED/TED group are relative to the Baseline prior to GATTEX exposure at the beginning of Study 020.

- The NT, PBO/TED group represents those subjects who either participated in Study 020 and received placebo, or who were eligible for randomization in Study 021 but qualified after the enrollment number was satisfied and entered Study 021 directly. These subjects therefore were first exposed to active treatment with GATTEX in Study 021. All observations reported for the NT, PBO/TED group are relative to the last visit before exposure to GATTEX in Study 021.

As this is an ongoing trial, efficacy data reported in this Section of the Briefing Document represent information collected at completed visits in the first 6 months (through Visit 6 of this extension study), which the majority of subjects have completed. Limited meaningful observations can be made beyond Visit 6 with regard to efficacy, as subjects may not have completed these visits.

A summary of the key efficacy results from ongoing Study 021 is provided below.

Efficacy Results for TED/TED

- The response to GATTEX observed after 24 weeks of treatment in Study 020 was maintained in the TED/TED group during continued, long-term treatment in the interim reporting period of the extension study, with reductions from Baseline in mean absolute PN/IV volume observed where completed visit information was available at Month 1, Month 3, and Month 6.

- After an additional 1 month of treatment with GATTEX 0.05 mg/kg/day during the interim report period, the mean (±SD) reduction in absolute PN/IV volume in the TED/TED group was 5.28±3.82 L/week from a Baseline level of 12.85 L/week, with a mean reduction of 40.65±21.55%.

- After an additional 3 months of treatment with GATTEX, the mean reduction in absolute PN/IV volume was 5.72±3.77 L/week from a Baseline level of 13.06 L/week, with a mean reduction of 45.80±22.68%.

- After an additional 6 months of treatment with GATTEX, the mean reduction in absolute PN/IV volume was 5.16±4.79 L/week from a Baseline level of 12.76 L/week, with a mean reduction of 34.18±56.65%. In one subject in the TED/TED group, PN/IV volume was increased to 13 L/week (representing a 221% increase) at the Month 6 visit because of a treatment-emergent SAE. That subject could therefore be considered an outlier. Thus, the median reduction in PN/IV volume of 4.38 L/week, representing a median 42% change may be a more appropriate statistic to assess the change in PN/IV volume.

- Of 34 subjects in Study 021 who have been treated with GATTEX for at least 1 year (6 months in 020 and 6 months in 021), 31 (72% of the original 43 subjects treated in Study 020) were determined to be clinical responders at 1 year (i.e., ≥20% reduction from baseline), including all 26 GATTEX responders in Study 020 and 6 of 9 subjects who did not meet responder status at month 6 in Study 020.

- Two subjects in the TED/TED group were completely weaned from PN/IV volume support.

- Long-term treatment with GATTEX resulted in an additional reduction in the number of days per week that parenteral nutrition was required. A reduction in PN/IV support of at least 2 days per week was achieved in 13 (of 34, 38%)

subjects after treatment with GATTEX for 1 year (vs. 8 of 39 subjects, 21% after 6 months in Study 020). A reduction in PN/IV support of at least 3 days was achieved in 8 (of 34, 24%) subjects after treatment with GATTEX for 1 year (vs. 4 of 39 subjects, 10%, after 6 months in Study 020).

- Taking into account changes in oral intake and urine output, the fluid composite effect was calculated, encompassing volumes of PN/IV, oral intake, and urine output (PN/IV + Oral Intake – Urine Output). At completed visits at 1, 3, and 6 months reductions in the fluid composite effect paralleled the changes in PN/IV volumes.
    - At the Month 1 visit, the mean reduction in the fluid composite effect was 5.78±6.18 L/week in the TED/TED group.
    - At the Month 3 visit, the mean reduction in the fluid composite effect was 5.75±6.81 L/week in the TED/TED group.
    - At the Month 6 visit, the mean reduction in the fluid composite effect was 5.78±6.55 L/week in the TED/TED group.
- The mean plasma citrulline level for the TED/TED group increased by 24.55±14.03 µmol/L (n=16) at Month 12 in Study 021, from a Baseline level of 17.43±8.80 µmol/L.

Efficacy Results for NT, PBO/TED

- Signs of efficacy were also observed in subjects who had not received previous treatment with GATTEX in Study 020. Reductions from Baseline in mean absolute PN/IV volume in the NT, PBO/TED group were observed at 1, 3, and 6 month visits (for the first 6 months visits were less frequent [at 2 weeks, 1, 2, 3, and 6 months] compared to the first 6 months of Study 020).

- After 1 month of GATTEX treatment, the mean (±SD) reduction in absolute PN/IV volume in the NT, PBO/TED group was 0.97±1.80 L/week from a Baseline level of 11.70 L/week, with a mean reduction of 6.19±11.14%

- After 3 months of GATTEX treatment, the mean reduction in absolute PN/IV volume was 1.85±2.61 L/week from a Baseline level of 11.59 L/week, with a mean reduction of 13.43±25.89%

- After 6 months of GATTEX treatment, the mean reduction in absolute PN/IV volume in the NT, PBO/TED group was 2.19±3.045 L/week from a Baseline level of 11.70 L/week, with a mean reduction of 17.60±20.49%.

- After an initial 6 months of treatment with GATTEX, a 20% to 100% reduction from Baseline in weekly PN/IV volume was observed in 17 (of 43, 39.5%) subjects in the NT, PBO/TED group.

- One subject in the NT, PBO/TED group was completely weaned from PN/IV volume support (Table 23).

- At least a 1-day per week reduction (additional days off) was achieved at the Month 6 visit in 10 (of 43, 23.3%) subjects in the NT, PBO/TED group. Reductions of at least 2 days were achieved in 3 (7.0%) subjects, and reductions of at least 3 days were achieved in 2 (4.7%) subjects.

Conclusions from Long-term Extension Study 021

A durable treatment response was observed with GATTEX. Subjects in the TED/TED group maintained their response with reductions in PN/IV volume during the interim reporting period. As PN/IV volume reduction was maintained, a further benefit was observed in which more than 20% of subjects required up to 3 fewer days per week of PN/IV support. Two subjects in the TED/TED group were completely weaned from PN/IV volume support. Subjects receiving long-term treatment with GATTEX

experienced an increase in plasma citrulline, possibly indicating the presence of increased enterocyte mass.

Combined Long-term Efficacy Findings from Studies 005 and 021

The results from the completed long-term extension Study 005 (extension of Study 004) and the ongoing long-term extension Study 021 (extension of Study 020) provide evidence for the durability of treatment effect with GATTEX 0.05 mg/kg/day, without evidence for the development of tolerance during up to 1 year of follow-up. For Studies 004 and 005 there were 27 subjects on 0.05 mg/kg/day with data at Week 24 (end of Study 004), and 19 subjects at Week 52 (end of Study 005). For studies 020 and 021 there were 39 subjects with data at Week 24 (end of Study 020), and 34 subjects at Week 52 (6-month data in Study 021). Study 021 is currently ongoing. At the data cut-off (30 June 2011), all eligible subjects except one had data at Week 52 (34/35).

The results from the completed long-term extension Study 005 (extension of Study 004) and the ongoing long-term extension Study 021 (extension of Study 020) demonstrate the durability of the effect of GATTEX 0.05 mg/kg/day, without evidence for the development of tolerance during up to 1 year of follow-up (Table 32).

Table 32. Clinically Relevant Response with GATTEX 0.05 mg/kg/day – Studies 020/021 and 004/005 (Intent-to-Treat Population)

	Studies 020 & 021		Studies 004 & 005	
Study Week on GATTEX	**N**	**n (%)**	**N**	**n (%)**
24 (End of 004 & 020)	39	30 (76.9)	27	16 (59.3)
28 (4 weeks in 005 & 021)	37	32 (86.5)	23	17 (73.9)
32 (8 weeks in 005 & 021)	37	32 (86.5)	22	14 (63.6)
36 (12 weeks in 005 & 021)	36	35 (97.2)	21	14 (66.7)
52 (28 weeks in 005 & 021)	34	31 (91.2)	19	17 (89.5)

PN/IV=Parenteral nutrition/intravenous hydration

Note: Clinically relevant response defined as 20% to 100% Reduction from Baseline in PN/IV Volume.

Source: Study 020 CSR, Table 14.2.1.1; Study 021 CSR, Table 14.2.1.9; Study 004, Table 14.2.2.15; Study 005 CSR, Table 14.2.1.4

Table 33 summarizes mean change from Baseline PN/IV volume by visit with GATTEX 0.05 mg/kg/day in the long-term extension studies, providing additional evidence of durability of efficacy, and used to explore any signs of tolerance.

Table 33. Change from Baseline in Actual PN/IV Volume Used – Studies 020/021 and 004/005 (Intent-to-Treat Population)

Study Week on GATTEX	Studies 020 & 021		Studies 004 & 005	
	N	Mean Change from Baseline (L/wk)	N	Mean Change from Baseline (L/wk)
24 (End of 004 & 020)	39	-4.4	27	-2.5
28 (4 weeks in 005 & 021)	37	-5.3	23	-2.6
32 (8 weeks in 005 & 021)	37	-5.6	22	-2.9
36 (12 weeks in 005 & 021)	36	-5.7	21	-3.3
52 (28 weeks in 005 & 021)	34	-5.2	19	-4.9

L=liters, PN/IV=Parenteral nutrition/intravenous hydration
Source: Study 020 CSR, Table 14.2.2.1; Study 021 CSR, Table 14.2.1.1; Study 004 CSR, Table 14.2.3.5.2; Study 005 CSR, Table 14.2.1.1.3.1

Table 34 presents the number and percentage of subjects with at least a 1-, 2-, or 3-day reduction in the number of days of PN/IV support required per week compared with the Baseline level of weekly support. An assessment of additional days off of weekly PN/IV support provides further evidence of the durability of effect.

After 28 weeks of additional treatment in Study 021 (52 weeks total), 18 (of 34 subjects, 52.9%) had 1 or more additional days off. Furthermore, reductions of at least 2 days were achieved in 13 (of 34, 38.2%) subjects and reductions of at least 3 days were achieved in 8 (of 34, 23.5%) subjects.

Table 34. Summary of Subjects with a 1-, 2-, or 3-Day Reduction from Baseline in Days of PN/IV Per Week – Studies 020/021 and 004/005 (Intent-to-Treat Population)

Study Week on GATTEX	Studies 020 & 021		Studies 004 & 005	
	N	n (%)	N	n (%)
24 Weeks (End of 004 & 020)				
At Least a 1-Day reduction	39	21 (53.8)	27	8 (29.6)
At Least a 2-Day reduction	39	8 (20.5)	27	5 (18.5)
At Least a 3-Day reduction	39	4 (10.3)	27	3 (11.1)
52 Weeks (28 weeks in 005 & 021)				
At Least a 1-Day reduction	34	18 (52.9)	20	12 (60.0)
At Least a 2-Day reduction	34	13 (38.2)	20	6 (30.0)
At Least a 3-Day reduction	34	8 (23.5)	20	4 (20.0)

PN/IV=Parenteral nutrition/intravenous hydration
Source: Study 021 CSR, Table 14.2.1.13

Taken together, these data support the durability of the effect of GATTEX over up to 52 weeks of treatment. No signs of tolerance were observed. A clinically relevant response (≥20% reduction) was achieved in ~90% of subjects, resulting in PN/IV volume reduction of about 5 L/week (corresponding to a mean reduction of about 40% from baseline). Weekly PN/IV support was reduced by 1 or more days in 60% and 53% of subjects in Studies 005 and 021, respectively, after 52 weeks. A 2-day reduction in weekly PN/IV support was observed in 38.2% and 30.0% of subjects in the respective studies, and a 3-day reduction, in 23.5% and 20.0%, after 52 weeks.

The "plateau-like" effect (at ~5 L reduction from Baseline) occurred in the Studies 004/005 vs. 020/021, albeit at different time points most likely as result of the different weaning algorithms. This suggests that there is a new equilibrium to which each patient's enterocytes can be optimized, with no evidence of continued, uninterrupted GI hypertrophy. However, for individual subjects there continues to be further decreases

both in volume and number of days off PN/IV, even at 1 year, suggesting that further adaptation is occurring.

Appendix C. Additional Safety Tables

Table 35. Summary of Safety Assessments

Study Number	Adverse Events	Clinical Laboratory	ECGs	Vital Signs
006	Every Visit	Screening, Check-in, 24h, Follow-up	Screening, Check-in, 0h, 4h, 24h, Follow-up[b]	Screening, Check-in, 0h, 4h, 12h, 24h, Follow-up[b]
015	Every Visit	Screening, D0, D1, D4, D7	Screening, D0, D1, D4, D7, D8	Screening, D0, D1, D4, D7, D8
1621/13	Pre-dose, 2h, 12h, 24h, Day 8	Screening, Predose, Day 2, Day 8	Screening, Predose, 3h, 12h, 24h, Day 8	Screening, predose, 3h, 12h, 24h, Day 8
C09-001	Every Visit	Screening, Day 1 (predose and 24h postdose), End of Trial	Screening, Day -1, Day 1 (in triplicate for predose, 0h, 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h, 24h), End of Trial[b,c]	Screening, Day -1, Day 1 (predose, 12h and 24h postdose), End of Trial
017	Every Visit	Screening, Day 1 (predose), Day 1 (3h postdose), Day 2, Day 3, Follow-up	Screening, Day -1, Day 1 (predose), Day 1 (3h postdose), Follow-up[c]	Every Visit
018	Every Visit	Screening, Day -1, Day 2, Follow-up	Screening, D -1, D1 (predose, 1,2,4, 6, 8, 12h postdose), D2, Follow-up[c]	Every Visit
022	Every Visit[a]	Screening, Day -1, Days 1-8 (3h postdose), Day 9, Follow-up	Screening, Day -1, Day 1 (predose and 3h postdose), Day 4 (predose and 3h postdose), Day 8 (predose and 3h postdose), Follow-up[c]	Screening, Day -1, Days 1-8 (predose and 3h postdose), Day 9, Follow-up

Table 35. Summary of Safety Assessments (Continued)

Study Number	Adverse Events	Clinical Laboratory	ECGs	Vital Signs
C10-003	Every Visit	Screening, Check-in, Day 11 (plus CRP every day in clinic and at Follow-up)	Screening, Day 11	Screening, Check-in, Baseline, Day 1 to Day 11
92001	Every Visit[a]	Screening, Day 1, Day 7, Day 14, Day 21, Follow-up	Screening, Day 1, Day 7, Day 14, Day 21, Follow-up	Screening, Day 1, Day 7, Day 14, Day 21, Follow-up
004	Every Visit[a]	All visits but Stabilization	Screening, Baseline, W8, W16, W24, W28	All visits but stabilization
005	Every Visit[a]	Every Visit	Baseline, W8, W16-20, W28, Follow-up	Every Visit
008	Every Visit	Every Visit	Screening, W8, W12	Every Visit
009	Every Visit	Every Visit	Baseline, W12, W16	Every Visit
020	Every Visit	All visits but Stabilization	Screening, Baseline, W4, W24	Every Visit
021	Every Visit	Every Visit	Baseline, M1, M24	Every Visit

ECG=electrocardiograms, h=hour, M=month, W=week

a. Includes injection site reactions at post-baseline visits.

b. Check-in, 0h, 4h, 12h, and 24h refer to the time points within both treatment periods 1 and 2 of the study.

c. Day -1 and Day 1 refer to the time points within each of the 4 treatment periods of the study.

Table 36. Exposure to Study Drug – Placebo-Controlled SBS Studies (Safety Population)

Category	Study 020		Study 004			Studies 020 and 004			
	Placebo (N=43)	GATTEX 0.05 mg/kg/d (N=42)	Placebo (N=16)	GATTEX 0.05 mg/kg/d (N=35)	GATTEX 0.10 mg/kg/d (N=32)	Placebo (N=59)	GATTEX 0.05 mg/kg/d (N=77)	GATTEX 0.10 mg/kg/d (N=32)	All (N=109)
Duration of Exposure (wks)									
Mean (SD)	22.6 (5.11)	22.7 (5.98)	24.3 (1.28)	20.7 (7.96)	23.2 (5.63)	23.1 (4.46)	21.8 (6.98)	23.2 (5.63)	22.2 (6.62)
Min / Max	2.86 / 25.14	0.57 / 28.86	21.14 / 28.00	0.57 / 27.57	0.86 / 29.71	2.86 / 28.00	0.57 / 28.86	0.86 / 29.71	0.57 / 29.71
< 1 week, n (%)	0	2 (4.8)	0	1 (2.9)	1 (3.1)	0	3 (3.9)	1 (3.1)	4 (3.7)
1-< 4 weeks, n (%)	1 (2.3%)	0	0	3 (8.6)	0	1 (1.7)	3 (3.9)	0	3 (2.8)
4-< 8 weeks, n (%)	2 (4.7%)	1 (2.4)	0	1 (2.9)	1 (3.1)	2 (3.4)	2 (2.6)	1 (3.1)	3 (2.8)
8-<12 weeks, n (%)	0	0	0	0	0	0	0	0	0
12-<16 weeks, n (%)	0	0	0	2 (5.7)	1 (3.1)	0	2 (2.6)	1 (3.1)	3 (2.8)
16-<20 weeks, n (%)	1 (2.3%)	0	0	0	0	1 (1.7)	0	0	0
20-<24 weeks, n (%)	13 (30.2%)	9 (21.4)	2 (12.5)	5 (14.3)	1 (3.1)	15 (25.4)	14 (18.2)	1 (3.1)	15 (13.8)
≥24 weeks, n (%)	26 (60.5%)	30 (71.4)	14 (87.5)	23 (65.7)	28 (87.5)	40 (67.8)	53 (68.8)	28 (87.5)	81 (74.3)
Person-years of exposure	18.71	18.35	7.47	13.91	14.28	26.18	32.27	14.28	46.54

Max=maximum; Min=minimum; N,n=number; SD=standard deviation

Notes: Percentages are based upon the number of subjects in the Safety Population. Duration of exposure is defined as:
(last dose date - first dose date + 1) / 7. Person-years of exposure is defined as the total weeks of exposure for all subjects divided by 52 weeks.

Source: ISS, 4-Month Safety Update, Table 13

Table 37. Exposure to Study Drug – SBS Long-term Extension Studies (Safety Population)

Category	Placebo/ GATTEX 0.05 mg/kg/d (N=57)	Placebo/ GATTEX 0.10 mg/kg/d (N=7)	GATTEX 0.05/ GATTEX 0.05 mg/kg/d (N=62)	GATTEX 0.10/ GATTEX 0.10 mg/kg/d (N=27)
Duration of Exposure				
Mean weeks (SD)	44.7 (22.57)	25.8 (4.70)	42.6 (21.40)	25.5 (6.61)
Min / Max	1.00/89.86	15.4/28.57	1.86/103.1	4.14/30.71
<1 week, n (%)	0	0	0	0
1-<4 weeks, n (%)	3 (5.3)	0	1 (1.6)	0
4-<8 weeks, n (%)	1 (1.8)	0	1 (1.6)	1 (3.7)
8-<12 weeks, n (%)	3 (5.3)	0	1 (1.6)	2 (7.4)
12-<16 weeks, n (%)	1 (1.8)	1 (14.3)	3 (4.8)	0
16-<20 weeks, n (%)	0	0	0	0
20-<24 weeks, n (%)	1 (1.8)	0	1 (1.6)	3 (11.1)
24-<36 weeks, n (%)	8 (14.0)	6 (85.7)	21 (33.9)	21 (77.8)
36-<48 weeks, n (%)	12 (21.1)	0	10 (16.1)	0
≥48 weeks, n (%)	28 (49.1)	0	24 (38.7)	0
<3 months, n (%)	8 (14.0)	0	5 (8.1)	3 (11.1)
3 to <6 months, n (%)	2 (3.5)	2 (28.6)	3 (4.8)	3 (11.1)
6 to <12 months, n (%)	25 (43.9)	5 (71.4)	32 (51.6)	21 (77.8)
≥12 months, n (%)	22 (38.6)	0	22 (35.5)	0
Person Years of Exposure	48.97	3.47	50.79	13.24

Max=maximum; Min=minimum; N,n=number; SD=standard deviation

Notes: Percentages are based upon the number of subjects in the Safety Population. Duration of exposure is defined as: (last dose date - first dose date + 1) / 7. Person-years of exposure is defined as the total weeks of exposure for all subjects divided by 52 weeks.

Source: ISS, 4-Month Safety Update, Table 14

Table 38. Overall Summary of Treatment-Emergent Adverse Events Among GATTEX-Treated Subjects (Safety Population)

Parameter	Phase 3 SBS Studies (N=173)		All Studies (N=566)	
	n	(%)	n	(%)
Any treatment-emergent AE				
No	8	(4.6)	142	(25.1)
Yes	165	(95.4)	424	(74.9)
Treatment-emergent AE severity				
Mild	146	(84.4)	387	(68.4)
Moderate	138	(79.8)	228	(40.3)
Severe	78	(45.1)	115	(20.3)
Any treatment-emergent SAE	96	(55.5)	119	(21.0)
Treatment-emergent SAE severity				
Mild	26	(15.0)	28	(4.9)
Moderate	53	(30.6)	58	(10.2)
Severe	51	(29.5)	67	(11.8)
Treatment-emergent AEs leading to premature discontinuation	30	(17.3)	58	(10.2)
AEs leading to death	2	(1.2)	2	(0.4)

AE=adverse event; CRF= case report form, MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number; SAE=serious adverse event

Notes: Treatment-emergent AEs are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence. Values for relationship reported on the CRFs as possibly-related or probably-related are considered related, and values of unlikely-related are considered not related. Treatment-emergent AEs that do not have a relationship reported on the CRFs are considered related. All adverse events were coded using MedDRA version 12.0.

Source: ISS, 4-Month Safety Update, Table 38

Table 39. Overall Summary of Treatment-Emergent Adverse Events in SBS Subjects With ≥180 Days Exposure to GATTEX (Safety Population)

	GATTEX 0.05 mg/kg/d (N=109)		GATTEX 0.10 mg/kg/d (N=32)		All GATTEX (N=141)	
Parameter	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any treatment-emergent AE						
No	8	(7.3)	0		8	(5.7)
Yes	101	(92.7)	32	(100.0)	133	(94.3)
Treatment-emergent AE severity						
Mild	93	(85.3)	32	(100.0)	125	(88.7)
Moderate	87	(79.8)	27	(84.4)	114	(80.9)
Severe	43	(39.4)	13	(40.6)	56	(39.7)
Any treatment-emergent SAE	65	(59.6)	14	(43.8)	79	(56.0)
Treatment-emergent SAE severity						
Mild	17	(15.6)	7	(21.9)	24	(17.0)
Moderate	39	(35.8)	5	(15.6)	44	(31.2)
Severe	34	(31.2)	6	(18.8)	40	(28.4)
Treatment-emergent AEs leading to premature discontinuation	7	(6.4)	4	(12.5)	11	(7.8)
AEs leading to death	1	(0.9)	0		1	(0.7)

AE=adverse event; CRF= case report form, MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number; SAE=serious adverse event

Notes: Treatment-emergent AEs are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence. Values for relationship reported on the CRFs as possibly-related or probably-related are considered related, and values of unlikely-related are considered not related. Treatment-emergent AEs that do not have a relationship reported on the CRFs are considered related. All adverse events were coded using MedDRA version 12.0.

Source: ISS, 4-Month Safety Update, Table 43

Table 40. Summary of Treatment-Emergent Adverse Events Reported for ≥5% GATTEX-Treated Subjects With ≥180 Days GATTEX Exposure, in Descending Order – Long-term SBS Studies (Safety Population)

Preferred Term	GATTEX 0.05 mg/kg/day (N=109)	GATTEX 0.10 mg/kg/day (N=32)	All GATTEX (N=141)
Abdominal pain *	40 (36.7%)	11 (34.4%)	51 (36.2%)
Upper respiratory tract infection *	31 (28.4%)	9 (28.1%)	40 (28.4%)
Catheter sepsis *	29 (26.6%)	6 (18.8%)	35 (24.8%)
Nausea *	21 (19.3%)	11 (34.4%)	32 (22.7%)
Headaches *	18 (16.5%)	13 (40.6%)	31 (22.0%)
Injection site reactions *	15 (13.8%)	14 (43.8%)	29 (20.6%)
Asthenic conditions *	18 (16.5%)	8 (25.0%)	26 (18.4%)
Catheter site related reaction *	24 (22.0%)	2 (6.3%)	26 (18.4%)
Urinary tract infections *	21 (19.3%)	5 (15.6%)	26 (18.4%)
Abdominal distension	19 (17.4%)	5 (15.6%)	24 (17.0%)
Weight decreased *	21 (19.3%)	1 (3.1%)	22 (15.6%)
Febrile disorders *	20 (18.3%)	1 (3.1%)	21 (14.9%)
Musculoskeletal pain *	17 (15.6%)	4 (12.5%)	21 (14.9%)
Gastrointestinal stoma complication	17 (15.6%)	2 (6.3%)	19 (13.5%)
Fluid overload *	14 (12.8%)	4 (12.5%)	18 (12.8%)
Vomiting	11 (10.1%)	7 (21.9%)	18 (12.8%)
Flatulence	13 (11.9%)	4 (12.5%)	17 (12.1%)
Diarrhoea *	13 (11.9%)	3 (9.4%)	16 (11.3%)

Table 40. Summary of Treatment-Emergent Adverse Events Reported for ≥5% GATTEX-Treated Subjects With ≥180 Days GATTEX Exposure, in Descending Order – Long-term SBS Studies (Safety Population) (Continued)

Preferred Term	GATTEX 0.05 mg/kg/day (N=109)	GATTEX 0.10 mg/kg/day (N=32)	All GATTEX (N=141)
Hypersensitivity *	10 (9.2%)	6 (18.8%)	16 (11.3%)
Cognition and attention disorders and disturbances *	9 (8.3%)	4 (12.5%)	13 (9.2%)
Muscle spasms	10 (9.2%)	3 (9.4%)	13 (9.2%)
Dehydration	11 (10.1%)	1 (3.1%)	12 (8.5%)
Lower respiratory tract infection *	8 (7.3%)	4 (12.5%)	12 (8.5%)
Arthralgia	8 (7.3%)	3 (9.4%)	11 (7.8%)
Biliary tract disorder *	9 (8.3%)	2 (6.3%)	11 (7.8%)
Skin haemorrhage *	10 (9.2%)	1 (3.1%)	11 (7.8%)
Appetite disorders *	7 (6.4%)	2 (6.3%)	9 (6.4%)
Hepatic enzyme increased *	4 (3.7%)	5 (15.6%)	9 (6.4%)
Contusion	4 (3.7%)	4 (12.5%)	8 (5.7%)
Gastrointestinal stenosis and obstruction *	7 (6.4%)	1 (3.1%)	8 (5.7%)
Hot flush	8 (7.3%)	0	8 (5.7%)
Peripheral embolism and thrombosis*	8 (7.3%)	0	8 (5.7%)

MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number

Notes: Percentages are based upon the number of subjects in the Safety Population. Treatment-emergent adverse events are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence of System Organ Class and Preferred Term. All adverse events were coded using MedDRA version 12.0.

* Shows special interest in Body System or Organ Class. The preferred terms in the AE groupings represent medically similar terms.

Source: ISS, 4-Month Safety Update, Table 64

Table 41. Adverse Events by Time of Onset Reported for ≥5% GATTEX-Treated Subjects in Any Time Interval – SBS Studies (Safety Population)

Preferred Term of AE Grouping	<4 Weeks (N=173) n (%)	4-<12 Weeks (N=163) n (%)	12-<24 Weeks (N=156) n (%)	24-<36 Weeks (N=148) n (%)	36-<48 Weeks (N=123) n (%)	48-<72 Weeks (N=107) n (%)	≥72 Weeks (N=32) n (%)
Abdominal distension	13 (7.5)	12 (7.4)	2 (1.3)	3 (2.0)	0	1 (0.9)	0
Abdominal pain *	39 (22.5)	20 (12.3)	14 (9.0)	14 (9.5)	4 (3.3)	0	0
Asthenic conditions *	6 (3.5)	8 (4.9)	13 (8.3)	5 (3.4)	3 (2.4)	2 (1.9)	2 (6.3)
Catheter sepsis *	4 (2.3)	11 (6.7)	14 (9.0)	18 (12.2)	4 (3.3)	6 (5.6)	2 (6.3)
Catheter site related reaction *	2 (1.2)	8 (4.9)	8 (5.1)	2 (1.4)	6 (4.9)	3 (2.8)	2 (6.3)
Dehydration	2 (1.2)	3 (1.8)	1 (0.6)	4 (2.7)	1 (0.8)	1 (0.9)	2 (6.3)
Febrile disorders *	7 (4.0)	7 (4.3)	7 (4.5)	2 (1.4)	0	0	2 (6.3)
Fluid overload *	9 (5.2)	6 (3.7)	5 (3.2)	5 (3.4)	1 (0.8)	2 (1.9)	0
Gastrointestinal stoma complication	20 (11.6)	3 (1.8)	2 (1.3)	2 (1.4)	0	2 (1.9)	1 (3.1)
Headaches *	13 (7.5)	5 (3.1)	7 (4.5)	4 (2.7)	2 (1.6)	4 (3.7)	1 (3.1)
Hepatic enzyme increased *	0	0	2 (1.3)	8 (5.4)	2 (1.6)	0	0
Injection site reactions *	25 (14.5)	6 (3.7)	15 (9.6)	6 (4.1)	2 (1.6)	3 (2.8)	0
Musculoskeletal pain *	6 (3.5)	3 (1.8)	8 (5.1)	3 (2.0)	2 (1.6)	5 (4.7)	0
Nausea *	26 (15.0)	10 (6.1)	3 (1.9)	1 (0.7)	2 (1.6)	3 (2.8)	0
Peripheral embolism and thrombosis *	0	0	4 (2.6)	0	1 (0.8)	2 (1.9)	3 (9.5)
Skin haemorrhage *	2 (1.2)	3 (1.8)	2 (1.3)	2 (1.4)	2 (1.6)	0	2 (6.3)
Upper respiratory tract infection *	12 (6.9)	15 (9.2)	14 (9.0)	10 (6.8)	3 (2.4)	3 (2.8)	0

Table 41. Adverse Events by Time of Onset Reported for ≥5% GATTEX-Treated Subjects in Any Time Interval – SBS Studies (Safety Population) (Continued)

Preferred Term of AE Grouping	<4 Weeks (N=173) n (%)	4-<12 Weeks (N=163) n (%)	12-<24 Weeks (N=156) n (%)	24-<36 Weeks (N=148) n (%)	36-<48 Weeks (N=123) n (%)	48-<72 Weeks (N=107) n (%)	≥72 Weeks (N=32) n (%)
Urinary tract infections *	6 (3.5)	7 (4.3)	10 (6.4)	3 (2.0)	3 (2.4)	3 (2.8)	1 (3.1)
Weight decreased *	1 (0.6)	3 (1.8)	2 (1.3)	4 (2.7)	7 (5.7)	3 (2.8)	4 (12.5)

MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number

Notes: Percentages are based upon the number of subjects in the Safety Population. Treatment-emergent adverse events are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence of System Organ Class and Preferred Term. Subjects are included in the earliest interval in which an event occurred. All adverse events were coded using MedDRA version 12.0.

* Shows special interest in Body System or Organ Class. The preferred terms in the AE groupings represent medically similar terms.

Source: ISS, 4-Month Safety Update, Table 66

Table 42. Summary of Treatment-Emergent Adverse Events Reported for ≥5% of GATTEX-Treated Subjects in Descending Order – All Studies (Safety Population)

Preferred Term	All Studies (N=566) n (%)
Abdominal pain *	170 (30.0%)
Injection site reactions *	127 (22.4%)
Nausea *	103 (18.2%)
Headaches *	90 (15.9%)
Abdominal distension	78 (13.8%)
Upper respiratory tract infection *	67 (11.8%)
Asthenic conditions *	54 (9.5%)
Vomiting	50 (8.8%)
Musculoskeletal pain *	48 (8.5%)
Catheter sepsis *	44 (7.8%)
Cognition and attention disorders and disturbances *	44 (7.8%)
Constipation *	42 (7.4%)
Diarrhoea *	39 (6.9%)
Fluid overload *	39 (6.9%)
Gastrointestinal stoma complication	37 (6.5%)
Hypersensitivity *	36 (6.4%)
Flatulence	35 (6.2%)
Urinary tract infections *	35 (6.2%)
Febrile disorders *	34 (6.0%)
Hepatic enzyme increased *	31 (5.5%)

MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number

Notes: Percentages are based upon the number of subjects in the Safety Population. Treatment-emergent adverse events are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence of System Organ Class and Preferred Term. All adverse events were coded using MedDRA version 12.0.

* Shows special interest in Body System or Organ Class. The preferred terms in the AE groupings represent medically similar terms.

Source: ISS, 4-Month Safety Update, Table 59

Table 43. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug in Decreasing Frequency– All Studies (Safety Population)

Preferred Term	All Studies (N=566) n (%)
Number (%) of subjects with a treatment-emergent AE leading to premature discontinuation	58 (10.2%)
Abdominal pain	21 (3.7)
Abdominal distension	7 (1.2)
Crohn's disease	6 (1.1)
Nausea	6 (1.1)
Vomiting	5 (0.9)
Asthenia	2 (0.4)
Constipation	2 (0.4)
Foreign body trauma	2 (0.4)
Gastrointestinal stoma complication	2 (0.4)
Small intestinal obstruction	2 (0.4)
Alanine aminotransferase increased	1 (0.2)
Anal stenosis	1 (0.2)
Aspartate aminotransferase increased	1 (0.2)
Back pain	1 (0.2)
Blood alkaline phosphatase increased	1 (0.2)
Cachexia	1 (0.2)
Cardiac failure congestive	1 (0.2)
Catheter sepsis	1 (0.2)
Cerebrovascular accident	1 (0.2)
Cholelithiasis	1 (0.2)
Clonus	1 (0.2)
Coma	1 (0.2)
Cough	1 (0.2)

Table 43. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug in Decreasing Frequency– All Studies (Safety Population) (Continued)

Preferred Term	All Studies (N=566) n (%)
Decreased appetite	1 (0.2)
Dehydration	1 (0.2)
Depression	1 (0.2)
Dermatitis allergic	1 (0.2)
Dizziness	1 (0.2)
Drug level increased	1 (0.2)
Dysgeusia	1 (0.2)
Electrolyte imbalance	1 (0.2)
Fistula	1 (0.2)
Frequent bowel movements	1 (0.2)
Gastrointestinal dysplasia	1 (0.2)
Gastrointestinal motility disorder	1 (0.2)
Gastrointestinal tract adenoma	1 (0.2)
Haematochezia	1 (0.2)
Haemorrhoidal haemorrhage	1 (0.2)
Headache	1 (0.2)
Hypersomnia	1 (0.2)
Inflammatory bowel disease	1 (0.2)
Injection site erythema	1 (0.2)
Injection site pain	1 (0.2)
Injection site rash	1 (0.2)
Intestinal obstruction	1 (0.2)
Klebsiella bacteraemia	1 (0.2)
Lung squamous cell carcinoma stage unspecified	1 (0.2)
Metastatic neoplasm	1 (0.2)
Myalgia	1 (0.2)

Table 43. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug in Decreasing Frequency– All Studies (Safety Population) (Continued)

Preferred Term	All Studies (N=566) n (%)
Nasopharyngitis	1 (0.2)
Non-small cell lung cancer	1 (0.2)
Oedema peripheral	1 (0.2)
Pallor	1 (0.2)
Pancreatitis	1 (0.2)
Perirectal abscess	1 (0.2)
Sepsis	1 (0.2)
Spinal compression fracture	1 (0.2)
Syncope	1 (0.2)

AE=adverse event; MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number

Notes: Treatment-emergent AEs are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence of Preferred Term. All adverse events were coded using MedDRA version 12.0.

Source: ISS, 4-Month Safety Update, Table 53

Table 44. Summary of Treatment-Emergent Serious Adverse Events Reported in ≥2 GATTEX-Treated Subjects in Decreasing Frequency – All Studies (Safety Population)

Preferred Term	All GATTEX (N=566)
Subjects with ≥1 treatment-emergent SAE	119 (21.0%)
Catheter sepsis *	40 (7.1%)
Gastrointestinal stenosis and obstruction *	10 (1.8%)
Biliary tract disorder *	8 (1.4%)
Crohn's disease	7 (1.2%)
Lower respiratory tract infection *	7 (1.2%)
Catheter site related reaction *	6 (1.1%)
Febrile disorders *	6 (1.1%)
Peripheral embolism and thrombosis *	6 (1.1%)
Abdominal pain *	5 (0.9%)
Cognition and attention disorders and disturbances *	4 (0.7%)
Urinary tract infections *	4 (0.7%)
Cholestasis and jaundice *	3 (0.5%)
Dehydration	3 (0.5%)
Device dislocation	3 (0.5%)
Gastrointestinal stoma complication	3 (0.5%)
Intestinal haemorrhages *	3 (0.5%)
Pancreatic disorders nec *	3 (0.5%)
Cardiac failure congestive	2 (0.4%)
Cerebrovascular accident	2 (0.4%)
Device breakage	2 (0.4%)
Gastroenteritis	2 (0.4%)
Hepatic enzyme increased *	2 (0.4%)

Table 44. Summary of Treatment-Emergent Serious Adverse Events Reported in ≥2 GATTEX-Treated Subjects in Decreasing Frequency – All Studies (Safety Population) (Continued)

Preferred Term	All GATTEX (N=566)
Hypokalaemia	2 (0.4%)
Musculoskeletal pain *	2 (0.4%)

AE=adverse event; MedDRA=Medical Dictionary for Drug Regulatory Activities; N, n=number; SAE=serious adverse event

Notes: Treatment-emergent AEs are defined as any adverse event with a start date on or after the date of first dose and within 30 days after discontinuation of study drug. Subjects are counted no more than once for incidence of Preferred Term. All adverse events were coded using MedDRA version 12.0.

* Shows special interest in Body System or Organ Class. The preferred terms in the AE groupings represent medically similar terms.

Source: ISS, 4-Month Safety Update, Table 45

Table 45. Baseline and Change from Baseline at Endpoint for Liver Function Tests – Placebo-Controlled SBS Studies (Safety Population)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Alkaline phosphatase (IU/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	154.6	(94.5)	155.8	(83.3)	158.9	(78.5)	156.7	(81.6)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-9	(58.7)	-21.2	(99.8)	-23.3	(67.0)	-21.8	(91.0)
ALT (SGPT) (IU/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	41.8	(31.5)	44.6	(30.8)	50.2	(35.7)	46.2	(32.3)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.6	(17.7)	-12.2	(20.1)	-8.7	(32.1)	-11.2	(24.1)
AST (SGOT) (IU/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	34.4	(19.1)	34.9	(18.7)	41.1	(21.8)	36.7	(19.8)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	1.6	(19.4)	-6.1	(11.8)	-5.5	(22.7)	-5.9	(15.7)

Table 45. Baseline and Change from Baseline at Endpoint for Liver Function Tests – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Total Bilirubin (µmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	10.2	(7.8)	11.5	(9.4)	12.8	(21.8)	11.8	(14.1)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	2.5	(7.7)	-2.3	(5.8)	-2.4	(11.9)	-2.3	(8.0)
GGT (IU/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	85.8	(78.4)	76	(66.4)	78.9	(83.8)	76.9	(71.6)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-4.2	(43.0)	-11.5	(42.9)	5.8	(59.3)	-6.4	(48.7)

Studies included 004 and 020.

ALT=alanine aminotransferase, AST= aspartate aminotransferase), GGT=gamma glutamyl transpeptidase
Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment that is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit).

Source: ISS, 4-Month Safety Update, Table 10.1.2

Table 46. Baseline and Change from Baseline at Endpoint for Renal Function Tests – Placebo-Controlled SBS Studies (Safety Population)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
BUN (mmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	6.57	(3.45)	6.17	(2.35)	6.15	(2.16)	6.17	(2.29)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.32	(2.06)	-0.48	(1.98)	-0.18	(1.82)	-0.39	(1.93)
Creatinine (µmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	88.6	(30.4)	83.5	(27.5)	82.8	(19.7)	83.3	(25.4)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	0.5	(11.8)	0.6	(13.8)	-1.9	(12.9)	-0.2	(13.5)

Studies included 004 and 020.

Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment that is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit).

Source: ISS, 4-Month Safety Update, Table 10.2.2

Table 47. Baseline and Change from Baseline at Endpoint for Other Chemistry Tests – Placebo-Controlled SBS Studies (Safety Population)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Albumin (g/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	41.5	(4.4)	41	(4.2)	38.3	(3.9)	40.2	(4.2)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-1.6	(3.0)	-1.2	(3.3)	-1.0	(4.0)	-1.1	(3.5)
Amylase (IU/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	96.4	(56.5)	87.2	(46.4)	83.8	(32.5)	86.2	(42.6)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-3.4	(27.1)	2.0	(36.4)	-2.4	(25.2)	0.7	(33.4)
Bicarbonate (mmol/L)								
Baseline								
n	32		46		32		78	
Mean (SD)	23.52	(3.65)	21.47	(4.47)	21.71	(3.13)	21.57	(3.95)
Change from Baseline to Endpoint								
n	32		41		31		72	
Mean (SD)	-0.41	(2.59)	0.64	(4.12)	-0.62	(3.72)	0.09	(3.97)

Table 47. Baseline and Change from Baseline at Endpoint for Other Chemistry Tests – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Calcium (mmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	2.283	(0.120)	2.283	(0.132)	2.348	(0.114)	2.302	(0.130)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.029	(0.121)	-0.006	(0.148)	-0.022	(0.143)	-0.010	(0.146)
Chloride (mmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	104.6	(4.4)	105.5	(3.8)	104.8	(3.0)	105.3	(3.6)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	0.9	(4.2)	-0.7	(3.7)	-0.5	(3.5)	-0.6	(3.6)
C-reactive protein (g/m^3)								
Baseline								
n	53		73		32		105	
Mean (SD)	4.42	(6.33)	5.84	(12.28)	2.57	(4.85)	4.84	(10.66)
Change from Baseline to Endpoint								
n	53		70		31		101	
Mean (SD)	-1.08	(6.55)	1.43	(15.03)	2.04	(5.36)	1.61	(12.83)

Table 47. Baseline and Change from Baseline at Endpoint for Other Chemistry Tests – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Glucose (mmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	5.57	(1.05)	5.38	(1.11)	5.21	(0.73)	5.33	(1.01)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.26	(0.77)	0.15	(0.98)	0.07	(0.78)	0.13	(0.92)
Lipase (IU/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	46.5	(25.0)	38.4	(19.4)	54.9	(41.7)	43.2	(28.7)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	1.2	(18.8)	18.7	(65.1)	2.2	(30.2)	13.8	(57.4)
Magnesium (mmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	0.829	(0.150)	0.784	(0.107)	0.787	(0.086)	0.784	(0.101)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.024	(0.159)	-0.017	(0.090)	-0.009	(0.106)	-0.015	(0.095)

Table 47. Baseline and Change from Baseline at Endpoint for Other Chemistry Tests – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Phosphate (mmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	1.185	(0.198)	1.174	(0.211)	1.166	(0.193)	1.172	(0.205)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.053	(0.211)	-0.012	(0.254)	0.033	(0.284)	0.001	(0.263)
Potassium (mmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	4.43	(0.4)	4.36	(0.42)	4.28	(0.49)	4.34	(0.44)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.09	(0.49)	-0.05	(0.48)	0.13	(0.47)	0	(0.48)
Sodium (mmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	139.7	(3.9)	140.4	(2.8)	140.6	(2.8)	140.4	(2.8)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	0.1	(2.9)	0	(2.8)	-1.3	(3.1)	-0.4	(2.9)

Table 47. Baseline and Change from Baseline at Endpoint for Other Chemistry Tests – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Uric acid (µmol/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	271.83	(116.78)	259.45	(116.41)	260.06	(88.14)	259.63	(108.47)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	11.1	(59.19)	18.12	(72.59)	7.16	(65.53)	14.89	(70.45)

Studies included 004 and 020.

Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment that is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit).

Source: ISS, 4-Month Safety Update, Table 10.3.2

Table 48. Baseline and Change from Baseline at Endpoint for Hematology Tests – Placebo-Controlled SBS Studies (Safety Population)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Hemoglobin (g/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	126.9	(11.8)	127.4	(12.9)	126.5	(13.6)	127.1	(13.0)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-2.2	(8.8)	-1.4	(8.6)	-0.2	(10.4)	-1.0	(9.1)
Hematocrit (%)								
Baseline								
n	59		77		32		109	
Mean (SD)	38.53	(3.46)	38.71	(3.43)	38.63	(3.91)	38.69	(3.56)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.85	(2.84)	-0.2	(2.91)	0.32	(2.82)	-0.05	(2.88)
Platelets (10^9/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	212.5	(69.3)	216.8	(77.2)	230.7	(99.9)	220.9	(84.3)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	1.0	(48.9)	21.9	(53.6)	7.9	(53.8)	17.8	(53.8)

Table 48. Baseline and Change from Baseline at Endpoint for Hematology Tests – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
White Blood Cells (10^9/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	6.642	(2.129)	6.42	(2.519)	5.615	(2.201)	6.184	(2.447)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.485	(1.491)	0.350	(1.514)	0.654	(1.349)	0.44	(1.467)
Red Blood Cells (10^9/L)								
Baseline								
n	59		77		32		109	
Mean (SD)	4.258	(0.497)	4.240	(0.500)	4.309	(0.522)	4.260	(0.505)
Change from Baseline to Endpoint								
n	59		74		31		105	
Mean (SD)	-0.072	(0.300)	-0.001	(0.342)	0.071	(0.325)	0.020	(0.337)
Neutrophils (%)								
Baseline								
n	58		77		32		109	
Mean (SD)	64.79	(11.07)	64.76	(9.61)	63.42	(11.60)	64.36	(10.20)
Change from Baseline to Endpoint								
n	58		74		31		105	
Mean (SD)	-0.58	(9.47)	1.26	(7.28)	1.58	(9.88)	1.36	(8.09)

Table 48. Baseline and Change from Baseline at Endpoint for Hematology Tests – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Lymphocytes (%)								
Baseline								
n	58		77		32		109	
Mean (SD)	26.48	(10.46)	26.66	(8.67)	27.61	(10.95)	26.94	(9.35)
Change from Baseline to Endpoint								
n	58		74		31		105	
Mean (SD)	0.45	(7.98)	-1.44	(5.96)	-1.69	(8.90)	-1.51	(6.91)
Monocytes (%)								
Baseline								
n	58		77		32		109	
Mean (SD)	5.66	(1.62)	5.25	(1.68)	5.83	(1.82)	5.42	(1.74)
Change from Baseline to Endpoint								
n	58		74		31		105	
Mean (SD)	-0.13	(1.72)	0.53	(1.87)	0.37	(1.84)	0.49	(1.86)
Eosinophils (%)								
Baseline								
n	58		77		32		109	
Mean (SD)	2.35	(1.76)	2.59	(1.7)	2.54	(2.21)	2.58	(1.86)
Change from Baseline to Endpoint								
n	58		74		31		105	
Mean (SD)	0.33	(1.66)	-0.28	(1.28)	-0.22	(1.28)	-0.26	(1.27)

Table 48. Baseline and Change from Baseline at Endpoint for Hematology Tests – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Basophils (%)								
Baseline								
n	58		77		32		109	
Mean (SD)	0.63	(0.41)	0.75	(0.67)	0.59	(0.36)	0.71	(0.60)
Change from Baseline to Endpoint								
n	58		74		31		105	
Mean (SD)	0	(0.45)	-0.13	(0.68)	-0.07	(0.37)	-0.11	(0.61)

Studies included 004 and 020.

Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment that is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit).

Source: ISS, 4-Month Safety Update, Table 10.7.2

Table 49. Baseline and Change from Baseline at Endpoint for Vital Signs – Placebo-Controlled SBS Studies (Safety Population)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Systolic blood pressure (mmHg)								
Baseline								
n	59		77		32		109	
Mean (SD)	119.1	(17.5)	121.2	(20.3)	119.8	(17.8)	120.8	(19.5)
Change from Baseline to Endpoint								
n	59		75		31		106	
Mean (SD)	-2.1	(14.1)	0.6	(16.5)	-0.9	(15.7)	0.2	(16.2)
Diastolic blood pressure (mmHg)								
Baseline								
n	59		77		32		109	
Mean (SD)	73.8	(11.1)	74.6	(10.8)	71.9	(12.2)	73.8	(11.2)
Change from Baseline to Endpoint								
n	59		75		31		106	
Mean (SD)	-1.7	(8.4)	-0.7	(10.6)	-0.8	(12.7)	-0.8	(11.2)
Heart rate (beats/min)								
Baseline								
n	59		77		32		109	
Mean (SD)	73.5	(11.9)	78.7	(14.2)	74.5	(10.7)	77.4	(13.3)
Change from Baseline to Endpoint								
n	59		75		31		106	
Mean (SD)	-0.5	(10.4)	-0.3	(12.6)	0.5	(11.7)	0	(12.3)

Table 49. Baseline and Change from Baseline at Endpoint for Vital Signs – Placebo-Controlled SBS Studies (Safety Population) (Continued)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Temperature (˚C)								
Baseline								
n	59		77		32		109	
Mean (SD)	36.45	(0.49)	36.38	(0.47)	36.46	(0.60)	36.4	(0.51)
Change from Baseline to Endpoint								
n	59		75		31		106	
Mean (SD)	-0.07	(0.46)	-0.04	(0.55)	0.09	(0.54)	0	(0.55)

Studies included 004 and 020.

Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment that is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit).

Source: ISS, 4-Month Safety Update, Table 11.1.2

Table 50. Baseline and Change from Baseline at Endpoint for Body Weight and BMI – Placebo-Controlled SBS Studies (Safety Population)

Parameter	Placebo (N=59)		GATTEX 0.05 mg/kg/day (N=77)		GATTEX 0.10 mg/kg/day (N=32)		All GATTEX (N=109)	
Weight (kg)								
Baseline								
n	59		77		32		109	
Mean (SD)	61.6	(11.81)	61.04	(10.26)	60.1	(10.07)	60.76	(10.16)
Change from Baseline to Endpoint								
n	59		75		31		106	
Mean (SD)	-0.26	(2.81)	0.96	(3.18)	1.32	(2.49)	1.06	(2.99)
BMI (kg/m^2)								
Baseline								
n	59		77		32		109	
Mean (SD)	22.15	(3.12)	21.84	(3.08)	21.94	(2.69)	21.87	(2.96)
Change from Baseline to Endpoint								
n	59		75		31		106	
Mean (SD)	-0.10	(1.01)	0.31	(1.07)	0.49	(0.92)	0.36	(1.03)

Studies included 004 and 020.

Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment that is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit).

Source: ISS, 4-Month Safety Update, Table 11.2.2

Table 51. Summary of Electrocardiogram Findings at Baseline and Endpoint – Placebo-Controlled SBS Studies (Safety Population)

Visit	Placebo (N=59)	GATTEX 0.05 mg/kg/day (N=77)	GATTEX 0.10 mg/kg/day (N=32)	All GATTEX (N=109)
Baseline				
n	59	77	32	109
Normal	44 (74.6%)	58 (75.3%)	24 (75.0%)	82 (75.2%)
Abnormal, NCS	15 (25.4%)	19 (24.7%)	8 (25.0%)	27 (24.8%)
Abnormal, CS	0	0	0	0
Endpoint				
n	57	74	30	104
Normal	47 (82.5%)	53 (71.6%)	21 (70.0%)	74 (71.2%)
Abnormal, NCS	10 (17.5%)	19 (25.7%)	9 (30.0%)	28 (26.9%)
Abnormal, CS	0	2 (2.7%)	0	2 (1.9%)

Studies included 004 and 020.

CS = Clinically Significant; NCS = Not Clinically Significant.

Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment that is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit). Electrocardiogram findings are based on the investigator's interpretation

Source: ISS, 4-Month Safety Update, Table 12.1.2

Appendix D. Subject Narratives

Subject 021-0155-1009, a 48-year-old male, was enrolled in Study 021 in the GATTEX 0.05 mg/kg/day group. The subject was in the stabilization/optimization phase in Study 020 but the study was closed when he was eligible for randomization. A SAE of "hepatic neoplasm" was reported on study day 326 (6/19/11) and was of 11 days' duration. Medical history included Crohn's disease, intestinal resection, Hodgkin's disease in 1988 treated with chemotherapy and radiation therapy, elevations in alkaline phosphatase and GGT since December 2009, and right hemicolectomy for cecal necrosis due to radiation. An ultrasound and CT scan performed on 21 January 2010 to determine the cause of the elevations in biliary enzymes revealed an enlarged liver with no focal lesions, an edematous gallbladder with dense bile, and 2 soft tissue foci of 10 and 15 mm diameter in the splenic field suspected to be accessory spleen. GATTEX was started on 29 July 2010. On 06 June 2011, after 313 days on GATTEX, the subject reported back pain. On 11 June 2011, an MRI was performed because of an increase in biliary enzymes and showed an extensive heterogeneous solid tumor with a diameter of up to 114 mm; the remaining liver parenchyma revealed solid tumors of varying size. Numerous lesions consistent with metastases were seen in the bodies of the visualized vertebrae and numerous enlarged retroperitoneal lymph nodes were noted. MRI of the lumbar spine revealed a compression fracture of L3. On 15 June 2011, a chest CT scan revealed numerous enlarged lymph nodes in the posterior mediastinum measuring up to 20 mm in their long axis, intralobular emphysema, and enlarged lymph nodes around the gastric cardia and abdominal aorta. Study drug was discontinued on 16 June 2011. Additional biochemistry revealed a normal alpha fetal protein and a markedly elevated carcinoembryonic antigen of >100 ng/mL (normal range 0-2.5 ng/mL). On 21 June 2011, a fine needle aspiration biopsy and core needle biopsy of the hepatic mass were performed and revealed metastatic adenocarcinoma, probably of GI origin. Primary therapy for the metastatic adenocarcinoma was not administered. The subject developed hepatic and renal failure and died on (b) (6) Autopsy on (b) (6) was inconclusive as to the primary site of the malignancy, but suggested it was intestinal. In addition, chronic myelogenous leukemia or acute myelogenous leukemia was suspected

by blood counts, but was not mentioned in the autopsy findings. Two expert radiologist consultants reviewed the subject's CT scans on 22 September 2011 and 06 October 2011, respectively. Both radiologists agreed that the CT of 21 January 2010, performed prior to GATTEX therapy, showed a small, approximately 2 cm low attenuation lesion in the left lobe of the liver seen only on the contrast images. Both agreed that the lesion could not be further characterized as benign or malignant based on the CT findings (data on file). The investigator considered the SAE to be related to treatment.

This subject developed a GI malignancy 22 years after receiving radiation therapy and chemotherapy for Hodgkin's disease. A high incidence of secondary malignancies after treatment for Hodgkin's disease has been increasingly encountered for decades, due to the high survival rates that began to be appreciated approximately 40 years ago (Bhatia et al, 2003; Ng et al, 2002). The risk of secondary malignancy increases with duration of follow-up and is highest among those who have received combination treatment consisting of radiation therapy and chemotherapy, as did this subject. The risk of developing a subsequent GI cancer is increased and is highest, with a relative risk of 18.7, among those treated at age 25 or younger, as was the case for this subject (Swerdlow et al, 2000). Additionally, a study conducted at Stanford University found that the relative risk of developing a secondary small intestinal malignancy was 11.6 in a cohort whose follow-up was 10.9 years (Birdwell et al, 1997). Based on the subject's history of radiation therapy and chemotherapy for Hodgkin's disease, his age when treated, and the duration of time from treatment, he was at high risk for developing a secondary malignancy, in particular, GI cancer.

Subject 021-0138-1011, a 64-year-old male, was enrolled in Study 021 in the GATTEX 0.05 mg/kg/day group (Study 020 placebo group). "Non-small cell lung carcinoma" was reported as a SAE on study day 85 (28 March 2011) and "lung neoplasm" reported on 29 March 2011. End dates for these AEs were not reported. Medical history included mesenteric artery thrombosis, intestinal resection, colectomy, MI, pulmonary embolism, atrial fibrillation, and tricuspid valve repair. The subject had smoked about 30 cigarettes per day for about 30 years. He was hospitalized on (b) (6) for a 2-week history

of hemoptysis. Chest CT revealed a tumor of the left lung and enlarged lymph nodes of the left pulmonary hilum, mediastinum, and peritracheal region. GATTEX was discontinued on 31 March 2011. Endobronchial biopsy revealed non-microcellular carcinoma, which the investigator assessed as squamous cell carcinoma, stage T2BN2M0. On 29 April 2011, the subject received chemotherapy including vinorelbine and carboplatin. Early study discontinuation occurred on 25 May 2011. The subject died on (b) (6) The cause of death was reported as non-small cell carcinoma of the lungs. An autopsy was not performed.

Subject 021-0138-1002, a 74-year-old male, was enrolled in Study 021 in the GATTEX 0.05 mg/kg/day group (Study 020 GATTEX 0.05 mg/kg/day group). An SAE of "lung squamous cell carcinoma stage unspecified" was reported initially as "hemoptysis" on treatment day 379 (3/21/11). Medical history included embolectomy of superior mesenteric artery, intestinal anastomosis, small intestinal resection, coronary artery disease, MI, GGT increased, and viral hepatitis. The subject had a history of cigarette smoking. A chest X-ray on that day was reported as being suspicious for an abscess. Chest CT scan performed on 3/23/11 was reported as having findings consistent with mycosis. Bronchoscopy was performed on 3/31/11 and an acid-fast bacilli test was reported to be negative for bacilli. The subject was started on INH, rifampin, and pyrazinamide on 4/14/11. On 8/29/11, a bronchoscopy was performed from which histopathology revealed planoepithelial (squamous cell) carcinoma of the right lung. GATTEX was discontinued on 8/26/11, and the subject discontinued study participation on 9/6/11.

Lung cancer in Poland was the second leading cause of death (8%) and the most frequent cause of cancer death (30%) in males in 2002 (Ramlau et al, 2006). The incidence of lung cancer in males in Poland was 85.2 per 100,000 in 2004. Considering the incidence of lung cancer by age, the rates were 376.9 and 516.9 per 100,000 for the age groups of Subject 021-0138-1002 and Subject 021-0138-1011, respectively (Szczuka and Roszkowski-Sliz, 2008). By contrast, the standardized incidence of lung cancer in white men in the USA was 75.2 per 100,000 from 2004 to 2008 (Howlader et al, 2011). These

later two subjects with lung cancer were SBS patients treated at this clinical site in Poland. Both subjects had a history of cigarette smoking.

In an Italian study Vantini *et al*. (2004), reported on the causes of death in 68 patients with intestinal failure (n=60 SBS, n=8 chronic idiopathic intestinal pseudo-obstruction) during a median follow-up period of 36 months (25th and 75th percentile in 12 and 60 months, respectively). Twenty-two patients died, 4 of them from new malignances, 2 of which were lung cancer.